CARBONYL-OLEFIN METATHESIS

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ABSTRACT

This review describes the development of strategies for carbonyl-olefin metathesis reactions relying on stepwise, stoichiometric, or catalytic approaches. A comprehensive overview of currently available methods is provided starting with Paternò-Büchi cycloadditions between carbonyls and alkenes followed by fragmentation of the resulting oxetanes, metal alkylidene-mediated strategies, [3+2]-cycloaddition approaches with strained hydrazines as organocatalysts, Lewis acid-mediated and Lewis acid-catalyzed strategies relying on the formation of intermediate oxetanes, and protocols based on initial carbon-carbon bond formation between carbonyls and alkenes and subsequent Grob-fragmentations. The review concludes with an overview of applications of these currently available methods for carbonyl-olefin metathesis in complex molecule synthesis. Over the past eight years, the field of carbonyl-olefin metathesis has grown significantly and expanded from stoichiometric reaction protocols to efficient catalytic strategies for ring-closing, ring-opening, and cross carbonyl-olefin metathesis. The aim of this review is to capture the status quo of the field and is expected to contribute to further advancements in carbonyl-olefin metathesis in the coming years.

CONTENTS

1. INTRODUCTION

The formation of carbon-carbon bonds is of fundamental importance in the field of synthetic chemistry and invaluable for the synthesis of many important biologically active molecules, including current pharmaceuticals and complex natural products. The development of new, sustainable, efficient, and selective catalytic procedures for carbon-carbon bond formation, therefore, represents a key research goal in synthetic chemistry. The metathesis reaction between two alkenes is among the most powerful catalytic carbon-carbon bond forming reactions available and has led to profound synthetic developments in the petroleum, materials, agricultural, and pharmaceutical industries.[1-13] The word metathesis, derived from the Greek words for "change" and "position," directly describes a chemical reaction which redistributes two subunits of two substrates. Olefin-olefin metathesis reactions are classified by a mechanistic profile that relies on olefins **1** and **2** and proceeds through an initial [2+2]-cycloaddition with a metal alkylidene **3** to form a cyclic 4-membered intermediate (Figure 1A). A subsequent [2+2]-cycloreversion forms two new alkene products **4** and **5** that each contain parts of the reactive partners **1** and **2**. Since its discovery, olefin-olefin metathesis has spurred important advances in the field of chemistry with broad implications for the synthesis of bioactive compounds and pharmaceuticals. In comparison, the corresponding carbonyl-olefin metathesis reaction between alkenes **1** and carbonyls **6** similarly enables carbon-carbon bond formation to result in new alkenes **4** (Figure 1B); however, this transformation remained, until recently, significantly less developed. Also referred to as a carbonyl-olefin exchange reaction[14-20] or oxametathesis[21-23] this review provides a comprehensive overview of currently available strategies for this transformation with a particular focus on viable substrate classes and accessible products. Specifically, this review has been organized to discuss the current status of each independent strategy to achieve carbonyl-olefin metathesis.

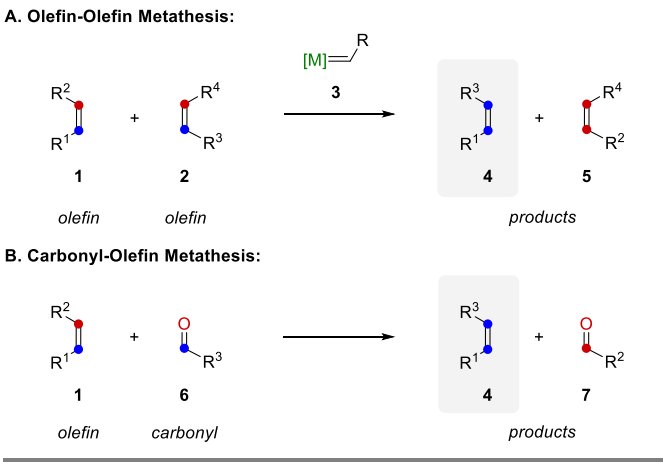


Figure 1. Olefin-Olefin Metathesis (A) versus Carbonyl-Olefin Metathesis (B).

The earliest reported protocols for carbonyl-olefin metathesis rely on a stepwise [2+2]-cycloaddition between alkenes **1** and carbonyls **6** following a Paternò-Büchi reaction protocol under UV-light irradiation to form oxetanes **8** (Figure 2A).[28] Fragmentation of **8** under elevated temperatures, acidic conditions, or electron transfer-induction results in alkenes **4** as the desired carbonyl-olefin metathesis products and carbonyls **7** as byproducts. An alternative approach for carbonyl-olefin metathesis is based on metal alkylidenes **9** following one of two strategies (Figure 2B): (1) Upon reaction of alkene **10** with a metal alkylidene **9**,

complex **11** is formed reminiscent of the initiation step in olefin-olefin metathesis. Subsequent carbonyl olefination with carbonyl **12** results in the desired alkene **14** and metal oxo-species **13**. Unfortunately, attempts for the reduction of **13** and its subsequent reintroduction to enable a catalytic process, remain unsuccessful, which renders this strategy stoichiometric in nature.[49,50] (2) Alternatively, the steps of carbonyl olefination and olefin metathesis can be reversed to first enable the reaction of carbonyl **12** with metal alkylidene **9** to form a new intermediate alkene **15** together with metal-oxo species **13**.[64] Olefin metathesis between alkenes **15** and **10** enabled by additional metal alkylidene **9** results in the desired carbonyl-olefin metathesis products **14**. Similarly to strategy I, the formation of metal oxo-species **13** renders strategy II stoichiometric in metal alkylidene reagent required. A third and distinct approach for carbonyl-olefin metathesis relies on α,β-unsaturated ketones **16** to provide polyconjugated polymers **18** upon reaction with tungsten-based reagents (Figure 2C).[14] The first catalytic strategy for carbonyl-olefin metathesis was based on a [3+2]-cycloaddition reaction paradigm between carbonyls **19** and unsaturated carbocycles **20** with hydrazine **21** as organocatalyst (Figure 2D). Carbonyl-olefin metathesis reactions following this design principle have been reviewed in 2019.[24] An alternative catalytic approach for carbonyl-olefin metathesis takes advantage of Lewis acids to activate carbonyls **19** for a [2+2]-cycloaddition with alkenes **1** to result in the formation of intermediate oxetane **23**, which upon activation with the Lewis acid undergo retro-[2+2]-cycloaddition to result in alkene **4** and carbonyl **7** as metathesis products (Figure 2E). These Lewis acid-based approaches have been reviewed in 2017[25] and 2018.[26] Importantly, all of these approaches are based on cycloaddition reactions that proceed either directly between carbonyl and alkene substrates, or between one of these starting materials and a suitable catalyst or reagent. A final strategy to achieve formal carbonyl-olefin metathesis reactions is instead centered on the initial formation of a carbon-carbon single bond between carbonyls **24** and alkenes **25** to access diols **26** as reactive intermediates, which can undergo a subsequent Grob fragmentation to form olefins **28** and acetone **27** as products.[140,143]

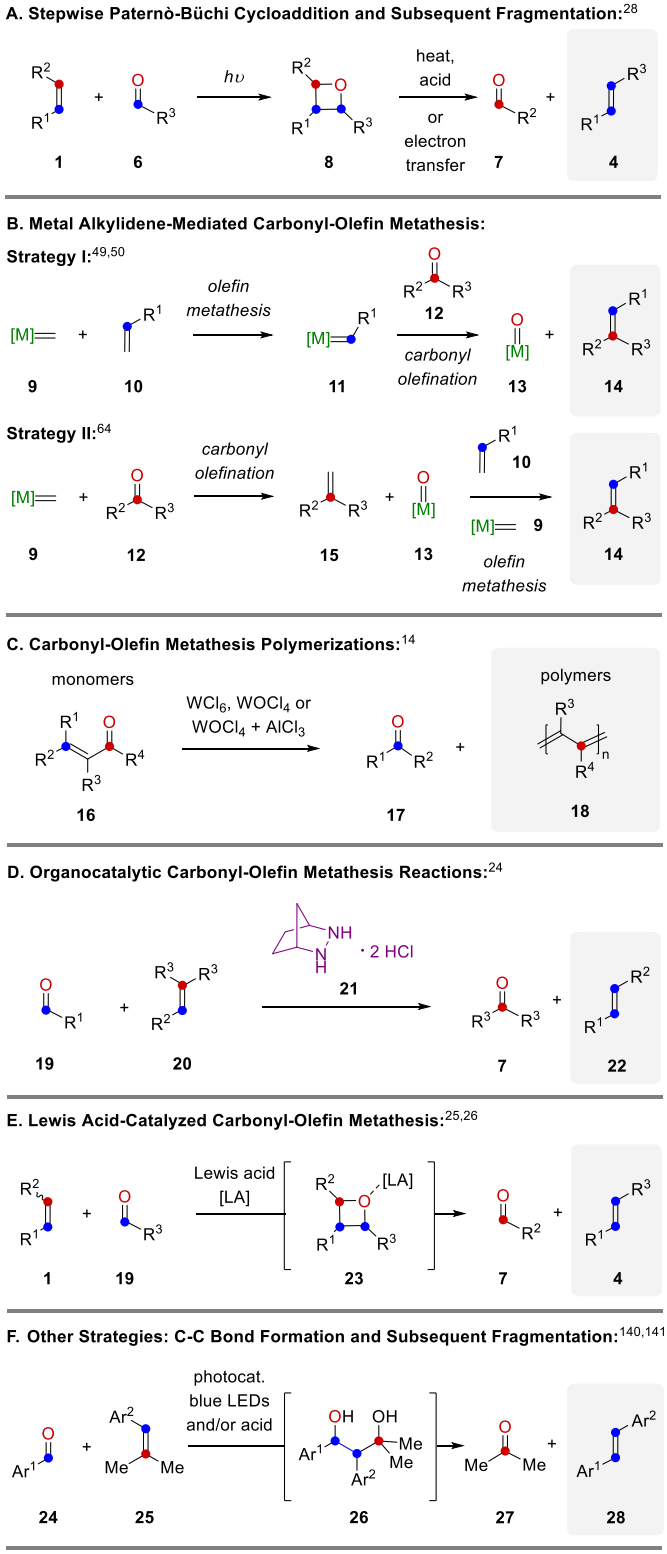


Figure 2. Overview of Currently Available Strategies for Carbonyl-Olefin Metathesis.

Although less advanced compared to olefin-olefin metathesis, developments in the field of carbonyl-olefin metathesis have grown significantly over the past decade. Importantly, categories of carbonyl-olefin metathesis reactions have been developed that are complementary to those of olefin-olefin metathesis and provide access to similar alkene products (Figure 3). Specifically, olefin-

olefin metathesis reactions are classified into three main categories including cross metathesis, ring-opening metathesis, and ring-closing metathesis (Figure 3A). Cross metathesis (CM) reactions between two alkenes **28** and **29** can form more functionalized alkenes **30** upon conversion with a suitable catalyst. Since olefin-olefin metathesis reaction are reversible, the controlled formation of product **30** can be challenging due to its ability to also function as a substrate in subsequent catalytic cycles. Ring-opening metathesis (ROM) reactions between linear alkenes **28** and cyclic alkenes **31** yield acyclic dienes **32** as products, taking advantage of the release of ring-strain as the driving force. The third category represents intramolecular, ring-closing metathesis (RCM) reactions of alkenes **33** to generate unsaturated products **34**. Additionally, two different strategies for polymerizations have been developed based on olefin-olefin cross and ring-opening metathesis. Particularly, ring-opening metathesis polymerizations (ROMP) are chain-growth, addition polymerization reactions of cyclic alkenes **35** driven by the release of ring strain while acyclic diene metathesis polymerizations (ADMET) are stepwise-growth, condensation polymerization reactions of terminal dienes **37** that result in polyenes **38** due to the favorable extrusion of ethylene gas as a metathesis byproduct.

The area of carbonyl-olefin metathesis has seen significant advances in recent years, and complementary strategies for cross, ring-opening, and ring-closing carbonyl-olefin metathesis have now been developed (Figure 3B). In comparison to olefin-olefin metathesis, carbonyl-olefin metathesis reactions are often irreversible, which is advantageous with regard to reaction design and achieving high yield and conversation. However, the substrate scope for carbonyl-olefin metathesis currently remains more limited compared to olefin-olefin metathesis. Most examples of cross carbonyl-olefin metathesis reactions (crossCOM) require aryl aldehydes **19** as substrates, which together with alkenes **29** form exclusively (*E*)-alkenes **30**. Similarly, ring-opening carbonyl-olefin metathesis (RoCOM) reactions are dependent on aryl aldehyde substrates **19** and cyclic alkenes **39** to form unsaturated ketones **40**. Ring-closing carbonyl-olefin metathesis reactions of unsaturated ketones **41** give access to 5-, 6-, and 7-membered ring systems **34**. In addition to these three categories for carbonyl-olefin metathesis, one strategy for polymerization has been reported based on cross metathesis of enones **16** resulting in polyenes **18** similar to ADMET in olefin-olefin metathesis. Finally, transannular carbonyl-olefin metathesis reactions of cyclic, unsaturated ketones **42** were developed following a ring-closing metathesis approach to result in ring-contraction products **43**.[27]

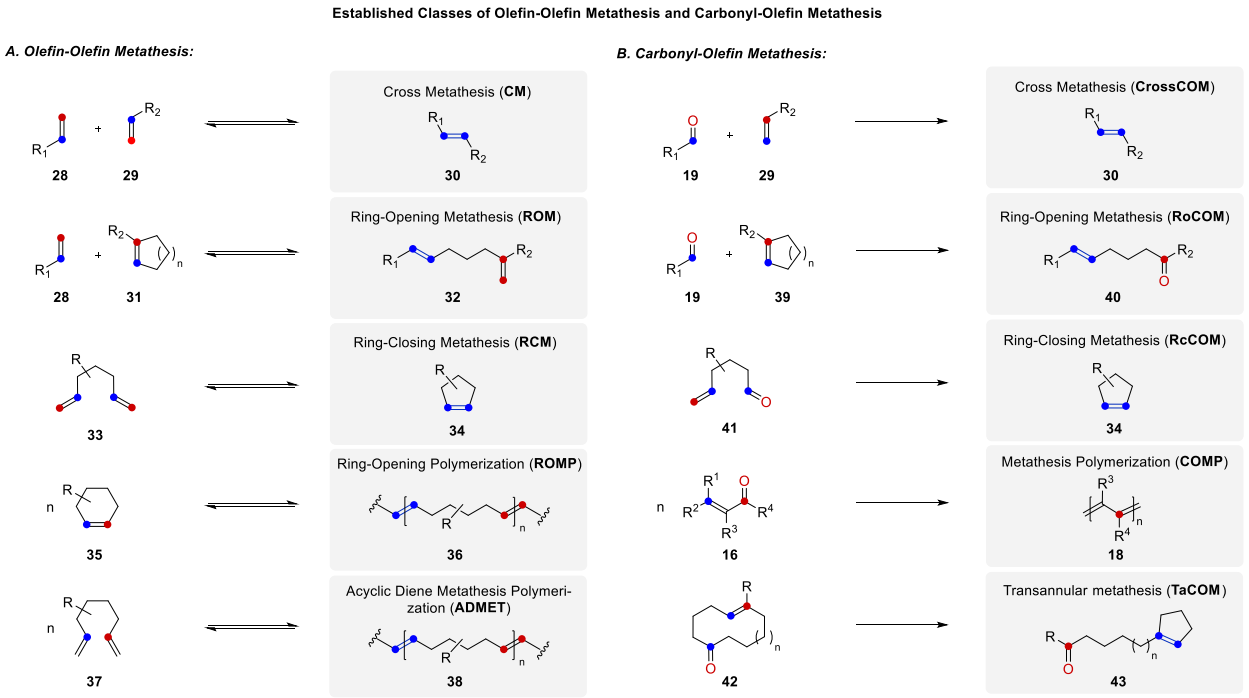
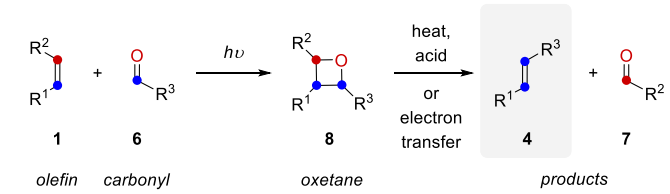


Figure 3. Classes of Olefin-Olefin Metathesis and Carbonyl-Olefin Metathesis Reactions Developed.

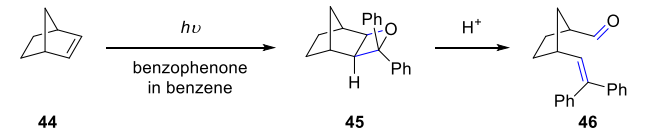
2. CARBONYL-OLEFIN METATHESIS VIA PATERNÒ-BÜCHI CYCLOADDITIONS AND SUBSEQUENT FRAGMENTATIONS

Scheme 1. Paternò-Büchi Reaction



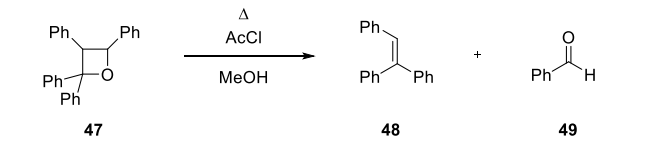
The earliest approaches to realize carbonyl-olefin metathesis take advantage of a two-step process between olefins **1** and carbonyls **6** upon photochemical irradiation following Paternò-Büchi reaction protocols (Scheme 1). Oxetane **8** is formed *via* a [2+2] photochemical cycloaddition, and subsequent fragmentation can be induced by an acid- or heat-mediated cycloreversion to provide the net carbonyl-olefin metathesis products alkene **4** and aldehyde **7**. Although this strategy represents the first approach to facilitate carbonyl-olefin metathesis reactions, its applications remain limited mostly due to a restricted substrate scope and functional group tolerance resulting from the harsh reaction conditions often requiring pyrolysis. This section outlines the developments, advancements, and insights gained regarding carbonyl-olefin metathesis reactions *via* Paternò-Büchi reactions in combination with fragmentation from the early, simple examples to more recent applications that allow for access to complex polycyclic compounds.

Scheme 2. Photo-Induced Oxetane Formation of Norbornene and Benzophenone by Scharf and Korte



In 1963, Scharf and Korte[28] investigated the photo-induced cyclodimerization of norbornene **44**. Following initial unsuccessful attempts to dimerize norbornene in the presence of UV light, aryl ketones were added as photosensitizers. The presence of benzophenone led to a new isolated product that was not the dimer of norbornene, but rather oxetane **45**, formed from the Paternò-Büchi reaction between norbornene and benzophenone (Scheme 2). The structure was confirmed by subjecting oxetane **45** to acidic conditions, which provided the fragmentation product **46** that was subsequently oxidized upon cleavage of the alkene fragment to the corresponding dicarboxylic acid. This overall transformation is a net ring-opening carbonyl-olefin metathesis reaction resulting in the formation of **46**, albeit serving the purpose of structural elucidation of oxetane **45**.

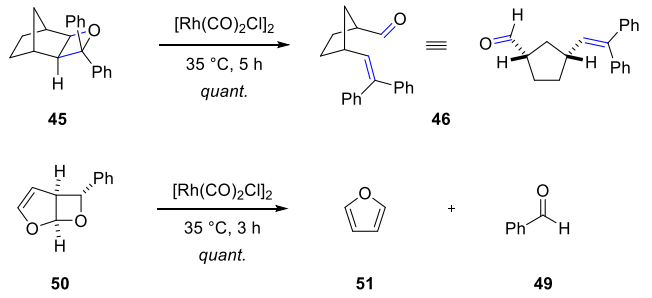
Scheme 3. Structural Elucidation of Oxetanes *via* Acid-Mediated Fragmentations by Kohler and Richtmeyer



Structural elucidation of oxetane **47** was performed previously by Kohler and Richtmeyer in 1930 (Scheme 3). The reaction of **47** with acetyl chloride in methanol at elevated temperatures resulted in the formation of alkene **48** and benzaldehyde **49**, which was confirmed upon conversion into the corresponding phenyl hydrazone.[29] Similarly, acid-mediated fragmentations of oxetanes formed upon UV irradiation of 2-methyl-2-butene with benzaldehyde, acetophenone, and *n*-butyraldehyde were used by Büchi and

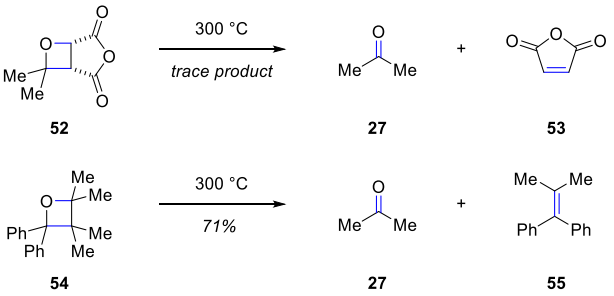
coworkers for the purpose of structure elucidations and mechanistic investigations of the initial [2+2]-cycloaddition between carbonyls and alkenes.[30]

Scheme 4. Rh(I)-Catalyzed Rearrangements of Vinyl Oxetanes by Grigg



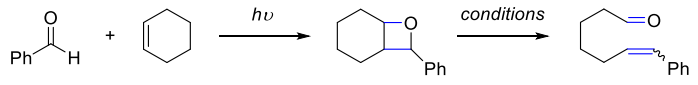
Oxetane fragmentation to carbonyl-olefin metathesis products has also been reported with catalytic amounts of Rh(I) complexes functioning as Lewis acids (Scheme 4).[31] Specifically, Grigg and co-workers investigated the rearrangements of epoxides and oxetanes in the presence of $[Rh(CO)_2Cl]_2$ and discovered that oxetane **45** fragments to provide **46**, quantitatively, incorporating a newly formed aldehyde and tri-substituted olefin. Likewise, oxetane **50** results in furan **51** and benzaldehyde **49** upon treatment under identical reaction conditions, albeit shorter reaction times (Scheme 4). Notably, the authors reported faster transformations when relying on CF_3CO_2H but a cleaner reaction profile with $[Rh(CO)_2Cl]_2$. The direction of the observed oxetane cleavage is predicted by the assumption that the coordination of the rhodium to the ether oxygen atom allows for fragmentation to form the most stable carbonium ion.

Scheme 5. Photolysis-Pyrolysis Sequence for Carbonyl–Olefin Metathesis by Jones



In 1973, Jones and co-workers first recognized the synthetic potential of this photolysis-pyrolysis sequence enabling carbonyl-olefin metathesis.[32] Their studies were focused on the specifics of oxetane decompositions while the reactive oxetanes were first formed *via* Paternò-Büchi cycloaddition reactions, which were then heated to 280-300 °C in diphenylmethane to induce fragmentation to the metathesis products (Scheme 5). The authors pointed out that while these transformations may also be performed under mild acid conditions, the pyrolysis route provides a clean product mixture with minimal side reactivity or decomposition. The pyrolysis results are consistent with the regioselective fragmentation of the weakest C-O bond in the rate-determining step, which the authors suggest could proceed *via* a concerted or stepwise reaction mechanism.

Scheme 6. Formation of Long-Chain Enals *via* Carbonyl-Olefin Metathesis by Jones

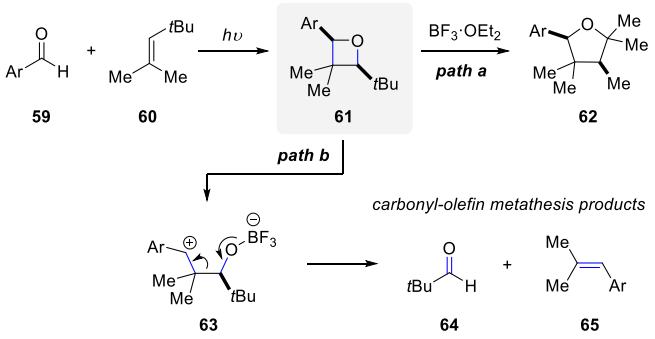


49 **56** **57** **58**

entry	reaction conditions	yield **58** (%)	cis/trans
1	G.l.c. injector port pyrolysis, 250°C	-	2:6
2	Flow pyrolysis, 400°C, 35 ml min^{-1}	23	2:6
3	Benzene-TsOH, 25°C	94	0:41
4	Benzene-$[Rh(CO)_2Cl]_2$, 80°C	70	0:31

In the following years, Jones and co-workers published the application of the photolysis-pyrolysis sequence for carbonyl-olefin metathesis toward the formation of long-chain enals.[33] The photolysis of benzaldehyde **49** and cyclohexene **56** allowed for isolation of oxetane **57** which under various thermolysis conditions provided good yields of *cis*- and tr*ans*-7-phenylhept-6-enal **58**, representing an overall ring-opening carbonyl-olefin metathesis reaction (Scheme 6). In the presence of catalytic acid or a Rh(I) complex that has been previously reported[17] for the fragmentation of oxetanes to metathesis products, *trans*-enal **58** was exclusively formed in 94% and 70% yields, respectively, with benzene as the solvent.

Scheme 7. Lewis Acid Fragmentation of Oxetanes by Carless

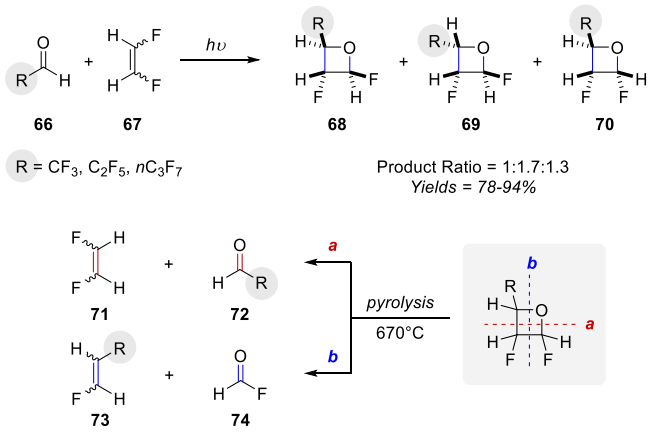


59 **60** **61** **62** **63** **64** **65**

entry	Ar	yield **62** (%)	yield **65** (%)
1	Ph	73	0
2	2-FC_6H_4	79	0
3	4-PhC_6H_4	20	70
4	2-MeC_6H_4	39	17
5	4-$MeOC_6H_4$	0	90
6	1-Naphthyl	0	20

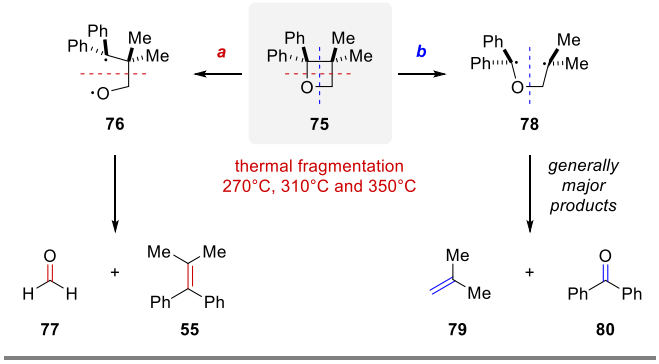
The Lewis acid-promoted fragmentation of oxetanes was reported by Carless and Trivedi in 1979[34] during their attempts towards the ring-expansion of oxetanes. Oxetane **61**, formed from aryl aldehyde **59**, provided ring expansion product **62** or the olefin product **65** in the presence of $BF_3 \cdot OEt_2$, resulting in a two-step metathesis reaction (Scheme 7). The ratio between ring expansion product **62** and the carbonyl-olefin metathesis product **65** was controlled by the electronic nature of the substituents on the aryl group of the aldehyde. Benzaldehyde and aryl aldehydes with electron-withdrawing groups were shown to promote pathway a for ring expansion, whereas electron-donating groups, such as methoxy groups, promoted exclusively pathway b, resulting in carbonyl-olefin metathesis products **64** and **65**. The authors suggested that the isolation of ring expansion product **62** supports the formation of intermediate carbocations upon treatment of oxetanes with protic and Lewis acids.

Scheme 8. Flow Pyrolysis of Fluorinated Oxetanes by Barlow, Coles, and Haszeldine



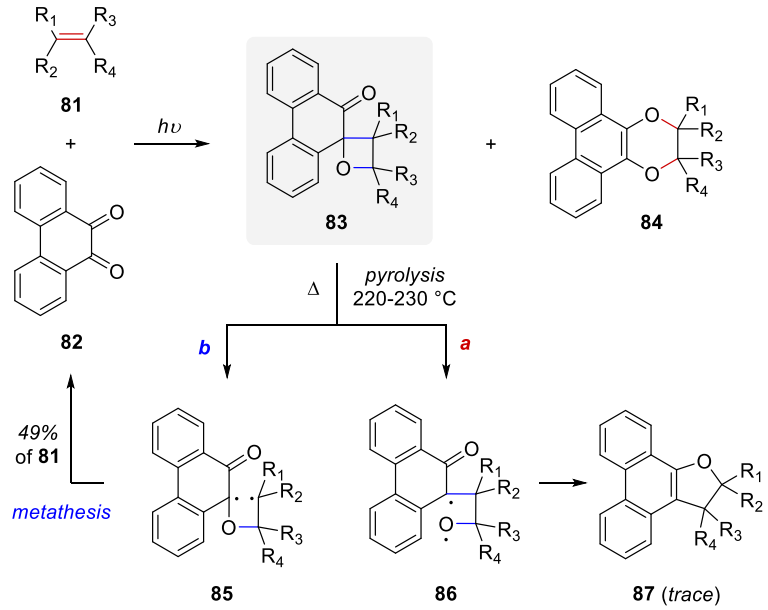
Barlow and co-workers reported the flow pyrolysis of fluorinated oxetanes at 670 °C.[35] Following the synthesis of a variety of fluorinated oxetanes **68**, **69**, and **70** in good yields *via* a Paternò-Büchi reaction of fluorinated aldehydes **66** and alkene **67**, pyrolysis was performed to provide carbonyl-olefin cross-metathesis products *via* fragmentation pathways a and b (Scheme 8). Interestingly, the flow pyrolysis fragmentation was not selective for the formation of *cis* or *trans* olefins but varied with changes in diastereoselectivity and substitution of the oxetane intermediate.

Scheme 9. Thermal Fragmentation 2-Aryl Substituted Oxetanes by Nishida



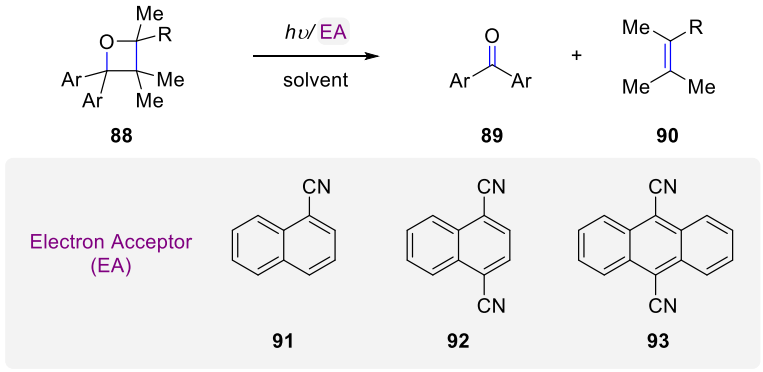
A qualitative study, which was reported in 1980[36], aimed to determine the conditions required to favor various fragmentation pathways of oxetanes **75**, taking into consideration that previous results obtained based on thermolysis protocols may have been altered by the presence of trace amounts of acid (Scheme 9). In order to determine if the fragmentation was entirely due to thermolysis and not trace acid for acid-catalyzed decomposition, N,N,N',N'-tetramethylenediamine (TMEDA) was used as the solvent based on previous reports of its beneficial use with extremely acid-sensitive compounds. Nishida and coworkers' observations are consistent with an earlier report by Jones[32] that fragmentation of **75** was indeed sensitive to the reaction conditions. Specifically, base treatment of solvent or the reaction vessel resulted in an increase of fragmentation pathway b leading to alkene **79** and benzophenone (**80**). Subsequent efforts of Nishida and coworkers centered on mechanistic investigations of oxetane fragmentation to differentiate between a biradical pathway and a possible concerted reaction path. The results obtained suggest that if a concerted fragmentation was feasible, it was not significantly favored over the diradical process.

Scheme 10. Pyrolysis of Keto Oxetanes by Maruyama



The formation of keto oxetanes **83** was reported in 1981[37] by Maruyama. Fragmentation of these oxetanes *via* pyrolysis in TMEDA (to avoid residual acid) provided two different products, olefin **81** and dihydrofuran **87** (Scheme 10). The starting materials, olefin **81** and diketone **82** were regenerated in an overall carbonyl-olefin metathesis reaction following a Paternò-Büchi reaction while the opposite fragmentation provided **87** as the rearranged product in trace amounts. This study also aimed to gain additional support for a radical-based oxetane fragmentation pathway by correlating the bond strengths in the oxetane ring to the structure of the possible intermediate biradicals and the observed results were consistent with the *s*-character of an intermediate carbon-centered radical.

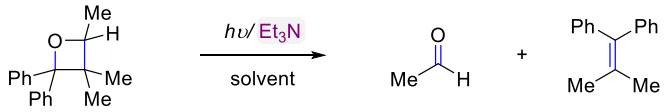
Scheme 11. Photosensitized Ring-Cleavage in the Presence of Electron Acceptors by Shima



entry	Ar	R	time (h)	yield **89** (%)	yield **90** (%)
1	p-ClC$_6$H$_4$	H	24	19	11
2	C$_6$H$_5$	H	20	27	20
3	C$_6$H$_5$	Me	24	31	24
4	**p-MeC$_6$H$_4$**	**H**	**10**	**55**	**55**
5	p-MeC$_6$H$_4$	Me	25	41	17
6	**p-MeOC$_6$H$_4$**	**H**	**4**	**80**	**71**

In 1989, Shima and co-workers[38] employed the use of photosensitizers for photoinduced ring cleavage in order to develop the regioselective and efficient cleavage of oxetanes. Previous studies of the fragmentation of oxetanes into carbonyl-olefin pairs had not focused on the factors that control regio- and stereochemical reaction outcomes. The ring cleavage was attempted with such electron acceptors as 1-cyanonaphthalene **91**, 1,4-dicyanonaphthalene **92**, and 9,10-dicyanoanthracene **93** (Scheme 11). Quantum yields for the fragmentation of aryl substituted oxetanes varied depending on the oxetane substitution and aryl groups of the photosensitizer. Notably, the quantum yield was increased with more electron-donating substituents on the oxetane. Yields of the carbonyl-olefin metathesis products, **89** and **90**, were improved for oxetanes containing aryl groups with electron-donating substituents such as *p*-Me or *p*-OMe (entries 4 and 6, Scheme 11).

Scheme 12. Photosensitized Ring-Cleavage in the Presence of an Electron Donor by Shima

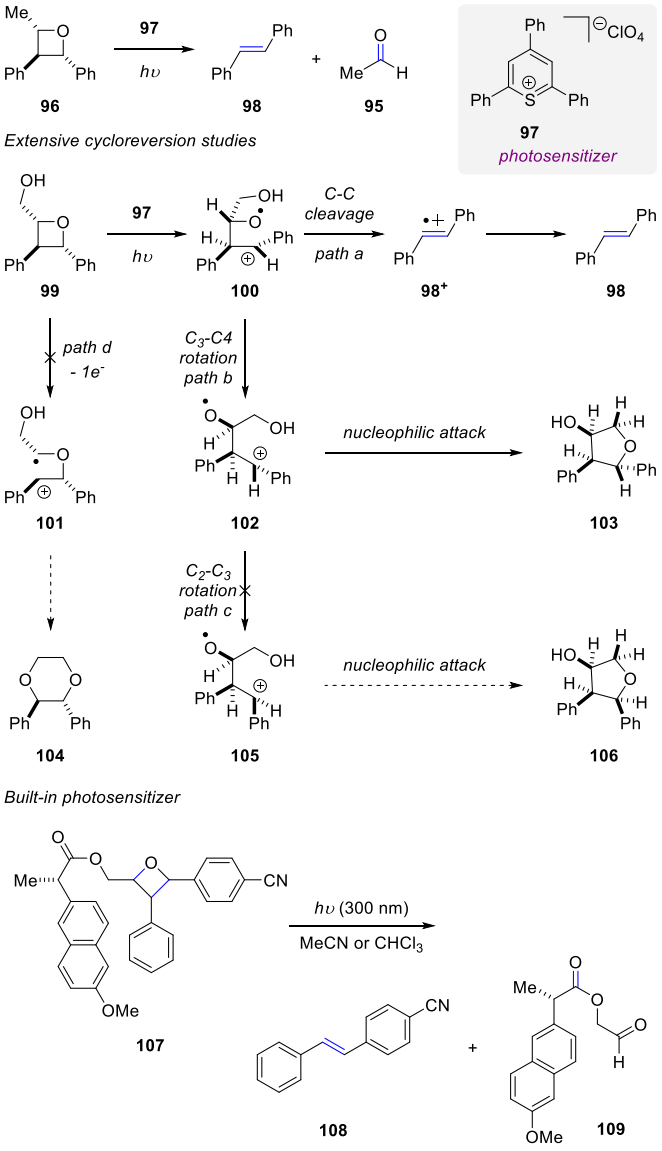


94 **95** **55**

entry	solvent	yield **55** (%)	conversion **94** (%)
1	hexanes	48	70
2	cyclohexane	50	68
3	dibutyl ether	64	67
4	THF	**73**	**51**
5	MeOH	24	66
6	MeCN	28	**57**

Shima and co-workers followed up on their initial report of regioselective oxetane fragmentation *via* photochemical electron transfer to aromatic nitriles as electron acceptors with an investigation into related oxetane fragmentations with an electron donor.[39] Importantly, the presence of trimethylamine functioning as electron donor resulted in the exclusive formation of 1,1-diarylethene product **55** (Scheme 12) while in contrast, the fragmentation in the presence of electron acceptors[38] had provided substituted benzophenones **89** and olefins **90** (Scheme 11). The reaction occurred most efficiently in nonpolar solvents, such as hexanes, but proceeded inefficiently in polar solvents suggesting the formation of an exciplex, as a coordinated complex, between the oxetane and triethylamine in the initiation process.

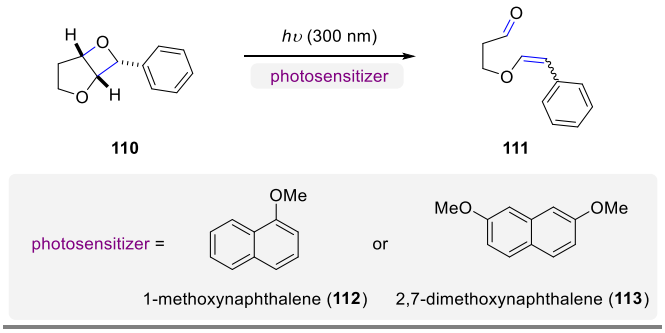
Scheme 13. Photochemical Cycloreversion of Methoxynaphthalene-Oxetane Dyads by Miranda



In 2002, Miranda and co-workers utilized photoinduced electron transfer (PET) of triaryl(thia)pyrylium salts (**97**) to promote cycloreversion of oxetane **96** yielding *trans*-stilbene **98** and acetaldehyde **95** (Scheme 13).[40] They quickly followed up on their initial report with extensive cycloreversion studies employing oxetane **99**.[41] The predominant electron transfer reaction occurred from the triplet excited state of photosensitizer **97**, followed by C-O bond cleavage to form **100**. Following path a, an additional C-C bond cleavage formed *trans*-stilbene radical cation **98**$^+$ and ultimately yielded *trans*-stilbene **98**. Miranda and co-workers also observed the formation of **103**, which is hypothesized to arise through path b, where rotation of the C_3-C_4 bond created intermediate **102**, followed by intramolecular nucleophilic attack of the pendant alcohol. Potential products **104** and **106** were not observed over the course of their investigations, ruling out paths c and d as active mechanistic pathways. Miranda and co-workers[42] aimed to expand their previous work, and in 2005 achieved the cycloreversion of oxetane radical anions generated by PET. The formation of **109** resulted from a Paternò-Büchi reaction of *trans*-cinnamyl alcohol and *p*-cyanobenzaldehyde followed by esterification. Fragmentation to olefin **108** and carbonyl **109** was possible due to the "built-in" photosensitizer, 1-methoxynaphthalene, that was introduced *via* esterification of the oxetane intermediate prior to fragmentation. Interestingly, the choice of solvent, acetonitrile or

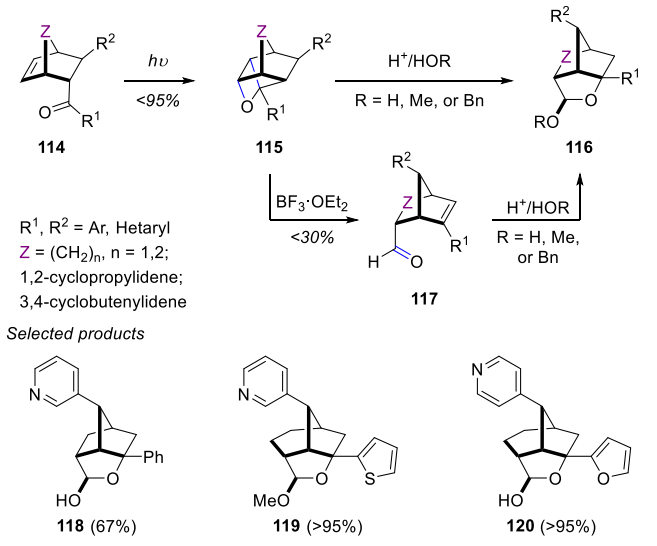
chloroform, provided distinct results. Acetonitrile as the solvent allowed for more efficient intramolecular fluorescence quenching, whereas stereodifferentiation was increased in chloroform indicating that one diastereomer was more conducive to fragmentation.

Scheme 14. Carbonyl-Olefin Metathesis of Bicyclic Oxetanes by Miranda and Griesbeck



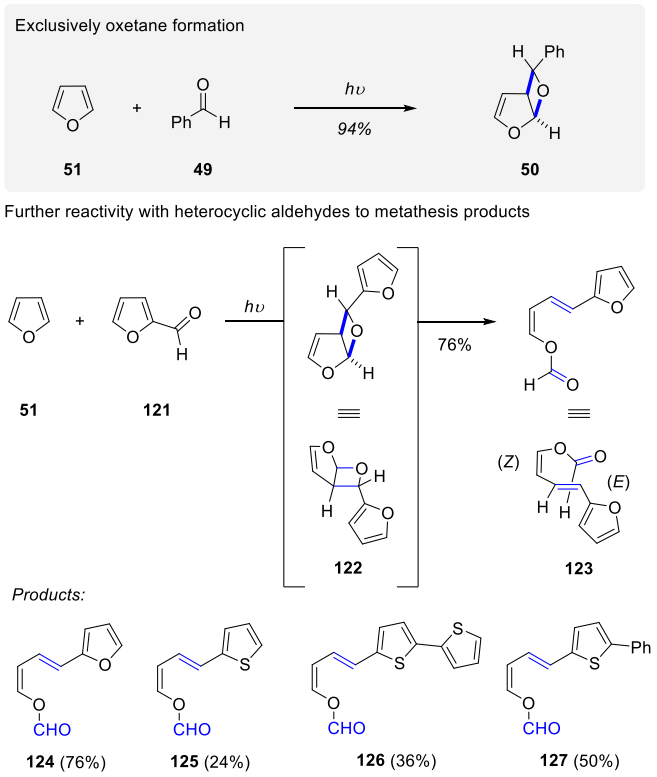
In 2006, Miranda, Griesbeck, and co-workers[43] reported the cleavage of bicyclic oxetane **110** obtained upon photocycloaddition of benzaldehyde and 2,3-dihydrofuran by means of reductive electron-transfer. They described this "metathesis" of oxetanes as an "attractive tool for the synthesis of new carbonyl-ene pairs" (Scheme 14). The cycloreversion of oxetane **110** was photoinduced by the electronically excited reductants in acetonitrile, which led to the formation of the carbonyl-olefin product **111** as a *trans/cis* mixture of isomers. Mechanistic studies determined that quenching rate constants were dependent on the substitution of the phenyl group and further investigation revealed that the reaction was exergonic in the case of substrates with electron-withdrawing groups. Product analysis established a "photo-photo metathesis" wherein both cycloaddition and cycloreversion were induced by photochemical processes.

Scheme 15. Photoprotolytic Oxametathesis in Polycyclic Systems by Kutateladze



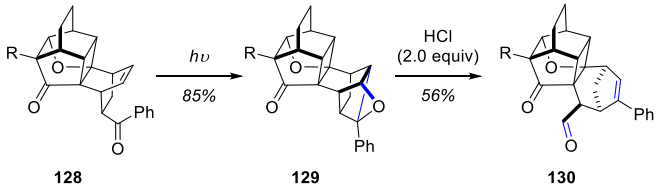
In 2009, Kutateladze and Valiulin[22] recognized the synthetic potential of acid-catalyzed oxetane fragmentations and decided to build on earlier work by Jones and coworkers.[33] Specifically, they developed a two-step sequence for carbonyl-olefin metathesis in which strained α-aryl and α-heteroaryl oxetanes **115** were formed and subsequently subjected to mild acid-catalyzed conditions to afford polycyclic aldehydes **117** or hemiacetals **116** (Scheme 15). This reaction design relied on the oxetane moiety itself being part of the strained intermediate formed to ultimately allow for access to a variety of diverse polycyclic systems from readily available starting materials.

Scheme 16. Oxetane Formation vs. Metathesis by D'Auria



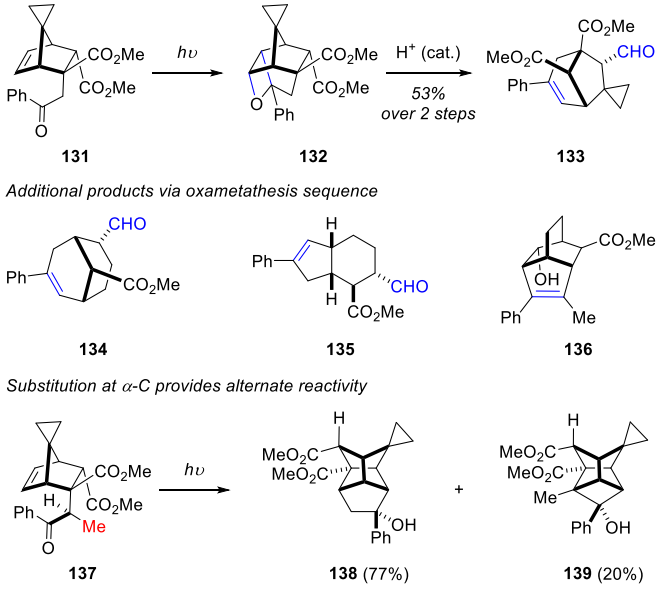
In 2010, D'Auria and co-workers[44] reported the metathesis reaction of furans and 2-substituted heterocyclic aldehydes *via* a proposed intermediate oxetane **122** (Scheme 16). The irradiation of **51** and **121** provided *Z,E*-olefin **123** as the exclusive product and the *Z,E*-olefin stereochemistry was observed for all other metathesis products observed (**124-127**). The selectivity of *Z*-olefin is set from **51** and the *E*-olefin arises from the fragmentation of the *exo*-oxetane intermediates (i.e. *exo*-**122**). Interestingly, tri-substituted heterocyclic aldehydes and non-arylated aldehydes provided exclusively oxetane products. The authors propose that the metathesis result of di-substituted heterocyclic aldehydes is due to possible participation of the π-aromatic orbitals in the oxetane C-O bond cleavage.

Scheme 17. Photoprotolytic Oxametathesis Leading to Molecular Complexity by Kutateladze



In 2011, Kutateladze and co-workers[23] reported a photoprotolytic carbonyl-olefin metathesis reaction that expedites the growth of molecular complexity over a few experimentally simple steps (Scheme 17). **128** was subjected to Paternò-Büchi reaction conditions to form oxetane **129** in 85% yield and the subsequent acid-catalyzed cycloreversion produces the alternative carbonyl-olefin pair metathesis product **130**. Interestingly, when oxetane intermediate **129** was subjected to acidic conditions, a byproduct also formed in the presence of excess acid (greater than 2.0 equivalents), in which the metathesis product underwent a second electrophilic addition of H^+ to the styrene moiety of **130** to generate a benzylic cation that was intercepted by an internal nucleophile, the enol.

Scheme 18. High-Yielding Photoprotolytic Oxametathesis in Polycyclic Systems by Kutateladze



A similar method for the construction of polycyclic systems was subsequently reported by Kutateladze in 2013.[24] This work expanded the two-step sequence with the photoinduced intramolecular formation of oxetanes and subsequent acid-catalyzed fragmentation to form carbonyl-olefin products (**134**-**136**, Scheme 18). Scheme 18 displays the formation of γ-oxetane **132** from acetophenone adduct **131** which subsequently transformed into the metathesis product **133** under acidic conditions. The incorporation of an α-methyl substituent in **137** provided a different reaction pathway that did not result in the carbonyl-olefin product, but rather a mixture of polycyclic compounds **138** and **139** with the stellane core as a result of a radical cyclization in which two C-C bonds were formed.

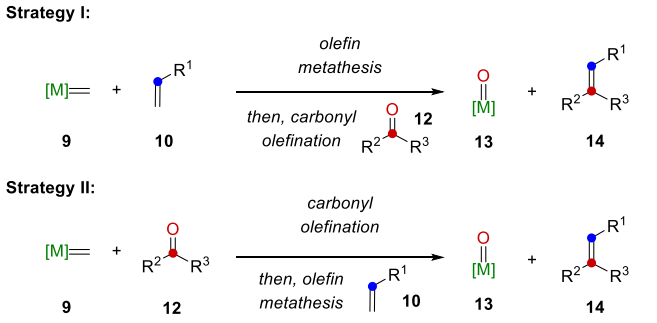
The ability to form and fragment oxetanes has been crucial in the pioneering and understanding of carbonyl-olefin metathesis reactions. Since the discovery of the Paternò-Büchi chemistry, UV light has been utilized to synthesize a variety of oxetanes and their fragmentation patterns have provided valuable insight. Mechanistic elucidations have revealed that from oxetanes, carbonyl-olefin metathesis can be promoted with acid, heat, or UV light to result in the desired alkene products. Limitations of this approach for carbonyl-olefin metathesis are dictated by current shortcomings in Paternò-Büchi reactions to form the required oxetanes, which include the requirement for high energy UV-light and a narrow scope of the carbonyl and alkene substrates. Concomitant to the development of oxetane formation and fragmentation sequences for carbonyl-olefin metathesis, metal-based approaches relying on metal alkylidenes were developed to access distinct alkene products.

3. METAL ALKYLIDENE-MEDIATED CARBONYL-OLEFIN METATHESIS.

Metal alkylidene complexes have been extremely successful in the formation of C-C bonds from the redistribution of two olefin fragments through the scission and regeneration of C-C double bonds, enabling olefin-olefin metathesis. These alkylidene catalysts have made profound impacts in the synthesis of molecules related to the petroleum, materials, agricultural, and pharmaceutical industries.[9] The capacity to perform these reactions catalytically is possible due to the ability for turnover of the metal alkylidene active catalyst with one of the olefin fragments following metathesis. The carbonyl-olefin metathesis reaction, however, when utilizing the same metal alkylidene complexes is unable to effect turnover of the metal alkylidene due to the resulting unreactive metal-oxo byproduct (**13**) formed following the initial metathesis reaction, thereby making these reactions stoichiometric (Scheme 19). For this reaction, these processes are not technically carbonyl-olefin metathesis reactions, because no new carbonyl is formed. Despite this inability to perform the carbonyl-olefin metathesis reaction catalytically with metal alkylidene complexes, the contributions to the field are nevertheless significant. Importantly, carbonyl additives have played an important role in ring-opening

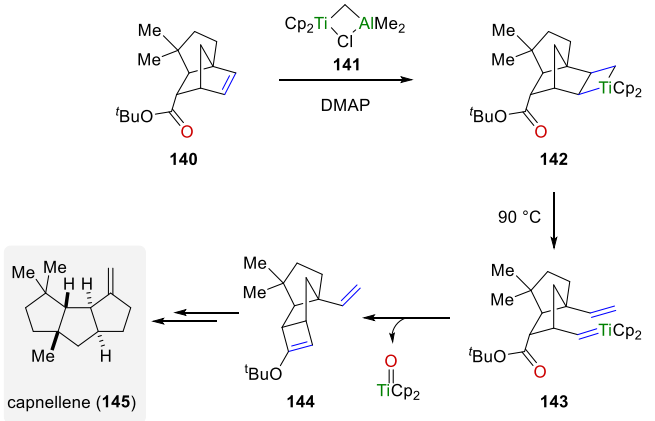
metathesis polymerization reactions with W- and Mo-alkylidene catalysts in order to terminate propagation, as the resulting metal-oxo species is unreactive.[45] Similarly, Grubbs and coworkers reported the trapping of titanium carbene species with ketones and aldehydes as a method to terminate the living polymerization of norbornene.[46] Furthermore, the vast majority of carbonyl-olefin metathesis reactions applied in complex molecule synthesis has thus far relied on metal-mediated approaches, which highlights the synthetic potential and importance that these transformations hold. Although stoichiometric in metal reagent, metal alkylidene-mediated approaches for carbonyl-olefin metathesis have seen important advances since an initial report by Grubbs in 1990. The developments in this area are highlighted in this part of the review with a particular focus on substrate scope and metal reagents used.

Scheme 19. Strategies for Metathesis with Metal Alkylidenes



Two strategies have been developed for carbonyl-olefin metathesis with metal alkylidene complexes. Strategy I relies on an initial olefin metathesis reaction between the metal alkylidene **9** and alkene **10** through a metallacyclobutane intermediate[47,48] (Scheme 19, Strategy I). Carbonyl olefination then occurs with the newly formed metal alkylidene and the carbonyl **12** to provide the desired olefin **14**, thereby completing the net carbonyl-olefin metathesis reaction. Strategy II employs the reverse reactivity in which carbonyl olefination occurs initially between metal alkylidene **9** and carbonyl **12** to form a metal-oxo byproduct and alkene intermediate, which then undergoes olefin metathesis with metal alkylidene resulting from **9** and alkene **10** to provide the net carbonyl-olefin metathesis product **14**.

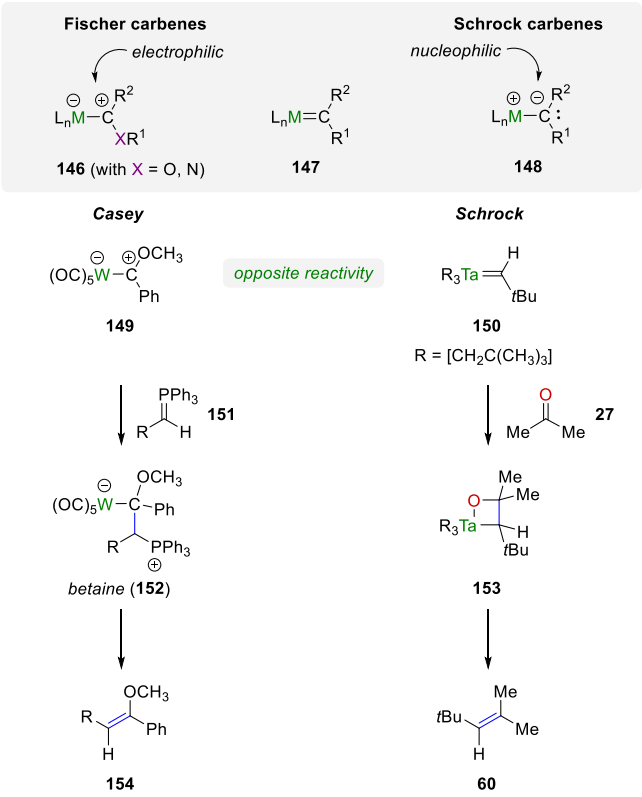
Scheme 20. Application of Strategy I by Grubbs



Stille and Grubbs were able to apply strategy I to the synthesis of capnellene (Scheme 20).[49,50] Bicyclic intermediate **140** was converted to metallacyclobutane **142** with titanaethylene **141**; subsequent heating initiated ring opening to **143** for an initial olefin metathesis reaction. Carbonyl olefination occurred with intramolecular trapping of the alkylidene with the proximal ester species

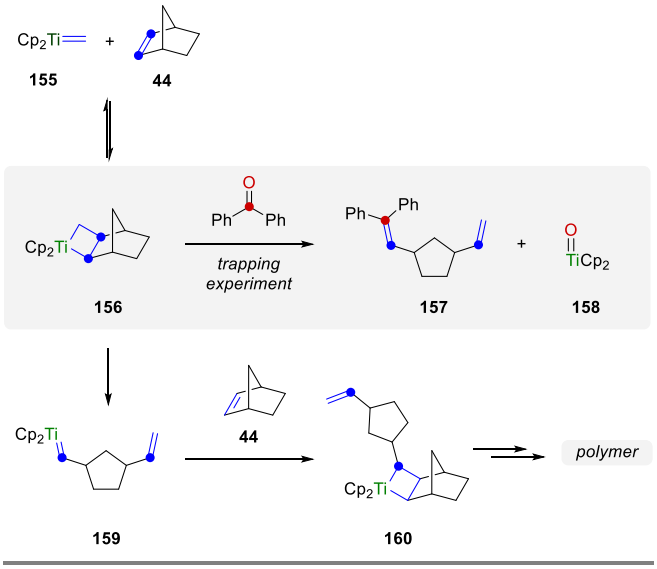
for the net carbonyl-olefin metathesis product **144**, which served as a key intermediate towards the total synthesis of (±)-Δ(9,12)-capnellene (**145**).

Scheme 21. Fischer and Schrock Metal-Carbenes



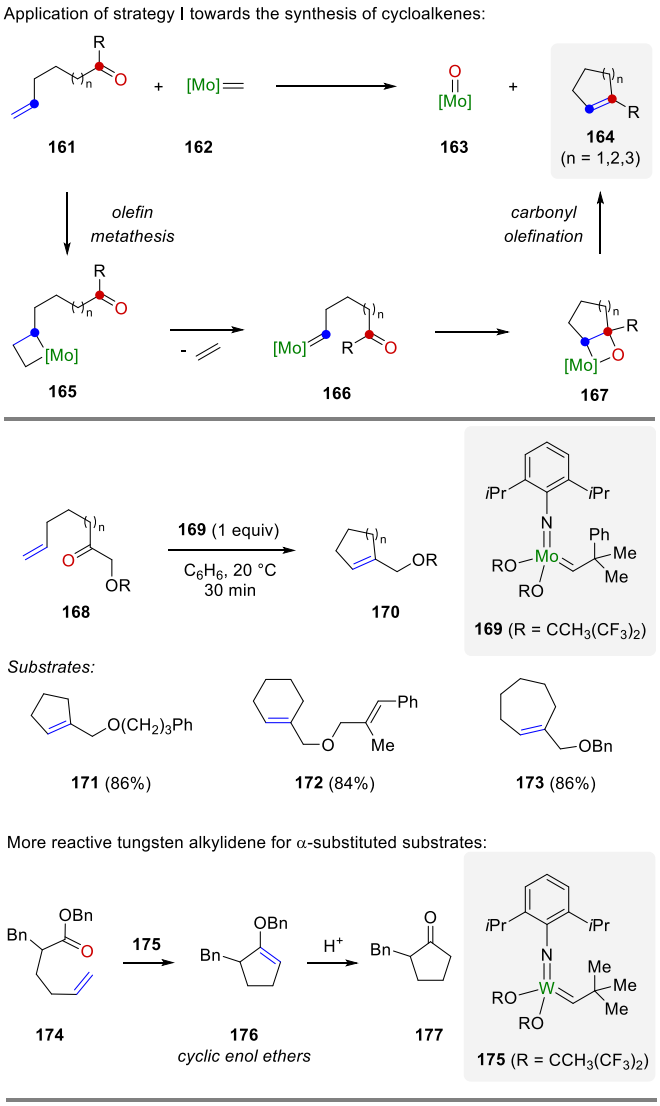
The use of either Fischer[51] (**146**) or Schrock[52] (**148**) metal-carbenes in "Wittig-like" reactions is well-known in the literature. Specifically, in 1972, phenylmethoxycarbenepentacarbonyltungsten(0) **149** was reacted with a carbon nucleophile **151** to form a betaine intermediate in which subsequent fragmentation provided the olefin product **154** (Scheme 21).[53] Conversely, $Ta[CH_2C(CH_3)_3]_3[CHC(CH_3)_3]$ (**150**)[54] used by Schrock[55] reacted with acetone in a nucleophilic manner to provide the oxametallocycle intermediate **153**, which fragmented to the desired olefin product **60**. This reactivity was similar to the use of the Tebbe[56,57] and Petasis[58] reagents whereby a metal-carbenoid reacted with a carbonyl to form a four-membered titanium oxide ring intermediate that fragmented to provide the methylenated product.

Scheme 22. Carbonyl-Olefin Metathesis Used for Endcapping Reactions of Polymers by Grubbs



The inherent reactivity of titanium carbene species with ketones and aldehydes[46,59] has been applied to ring-opening metathesis polymerization reactions (ROMP) for polymer cleavage to enable access to endcapped polymers and metathesis-inactive metal-oxo species **158** (Scheme 22). These living ROMP reactions were therefore quenched deliberately while installing a known moiety in place of the metal. Ethers have been commonly used for Ru-mediated polymerizations while carbonyls, such as benzaldehyde, have been employed for Mo- and W-mediated polymerizations.[45]

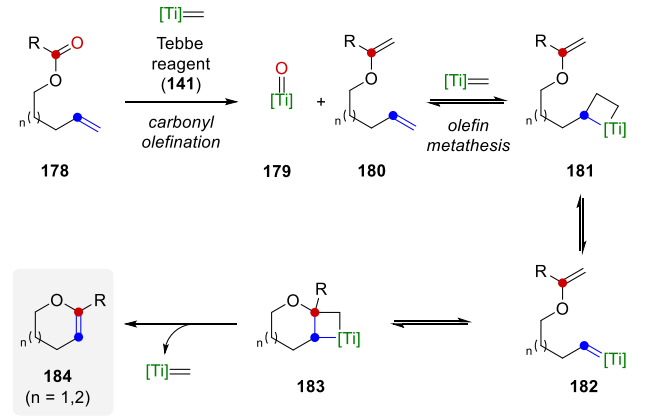
Scheme 23. Olefin Metathesis and Carbonyl Olefination by Grubbs

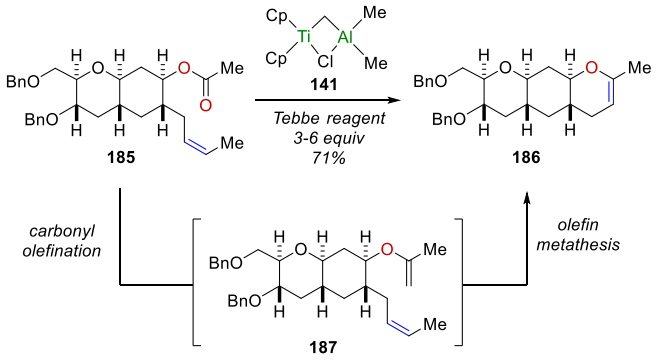


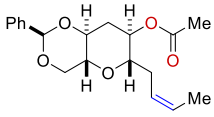
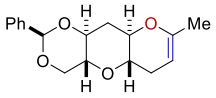
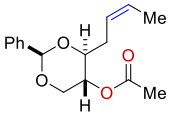
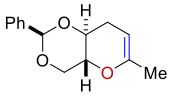
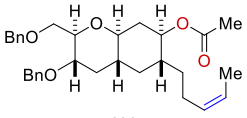
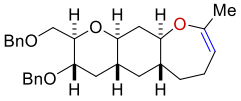
In 1993, Fu and Grubbs[60] reported a new method for alkylidene-mediated carbonyl olefination based on the initial discovery by Grubbs during studies toward the synthesis of capnellane[49,50] (Scheme 23). Following strategy I, the molybdenum alkylidene complex **162** initially undergoes a [2+2]-cycloaddition with **161** to form a metallacyclobutane intermediate **165**, followed by fragmentation to afford a new alkylidene **166**. This can then undergo a subsequent intramolecular carbonyl olefination to produce the desired cycloalkene **164**. The preference for an initial olefin metathesis reaction over the carbonyl olefination allowed for the ring-closing metathesis to occur instead of the formation of an acyclic diene. Stoichiometric amounts of the metal alkylidene **169** were required to provide a substrate scope with access to 5-, 6-, and 7-membered cycloalkenes (**171**, **172**, and **173**, respectively) in high yield. Initial attempts towards ring-closing metathesis employed a specific class of substrates (**174**) containing esters and α-substitution with the more reactive tungsten alkylidene **175** previously reported by Schrock.[61-63] The tungsten alkylidene complex formed cyclic enol ethers **176** that then reacted further to form cyclic ketones **177**.

Scheme 24. Application of Strategy II for the Conversion of Olefinic Esters to Cyclic Enol Ethers by Nicolaou

Application of strategy II towards the synthesis of cyclic ethers:





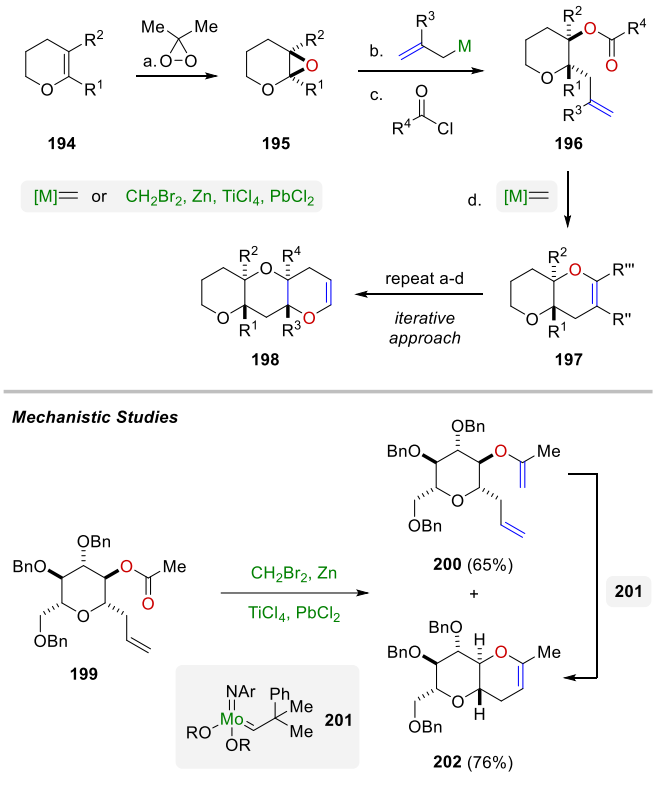
entry	substrate	reagent	product	yield (%)
1	 **188**	DT	 **191**	60%
2	 **189**	DT	 **192**	30%
3	 **190**	TR	 **193**	30%

TR = Tebbe Reagent, DT = Petasis Reagent: dimethyltitanocene (Cp_2TiMe_2)

A few years later, Nicolaou and co-workers reported a new method that utilized strategy II for the generation of cyclic enol ethers from olefins and esters using excess amounts of the Tebbe and Petasis reagents (Scheme 24).[64] The proposed mechanism begins with the initial formation of an acyclic enol ether **180** and oxo-titanium complex **179** through a carbonyl olefination reaction of **178** with the Tebbe reagent. Then, a second equivalent of the Tebbe reagent reacts to form the titanacyclobutane **181**. Subsequent fragmentation to afford the titanium alkylidene **182** then allows for an intramolecular cyclization to form a second titanacyclobutane **183**, which fragments to the desired cyclic enol ether metathesis product **184** *via* olefin metathesis. This method is able to generate

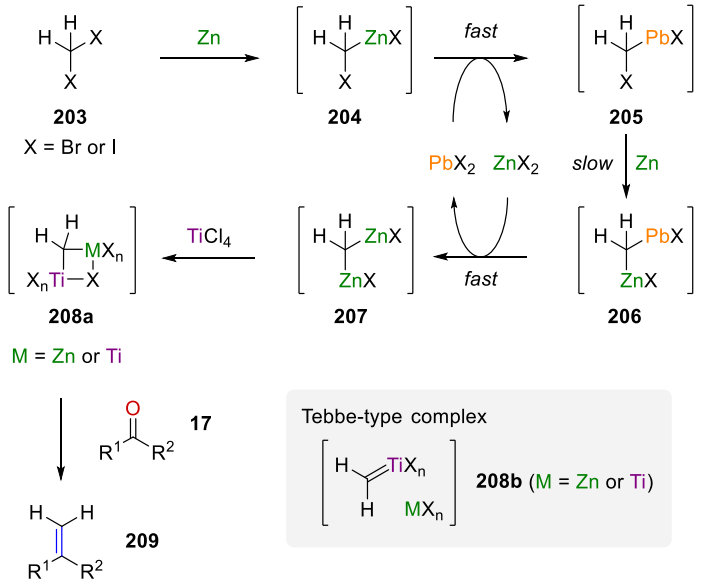
both 6- and 7-membered cyclic enol ethers (**191-193**) and is tolerant of a number of functional groups within the substrates (**188-190**).

Scheme 25. Iterative Pathway Towards Fused Ether Ring Systems by Allwein and Rainier



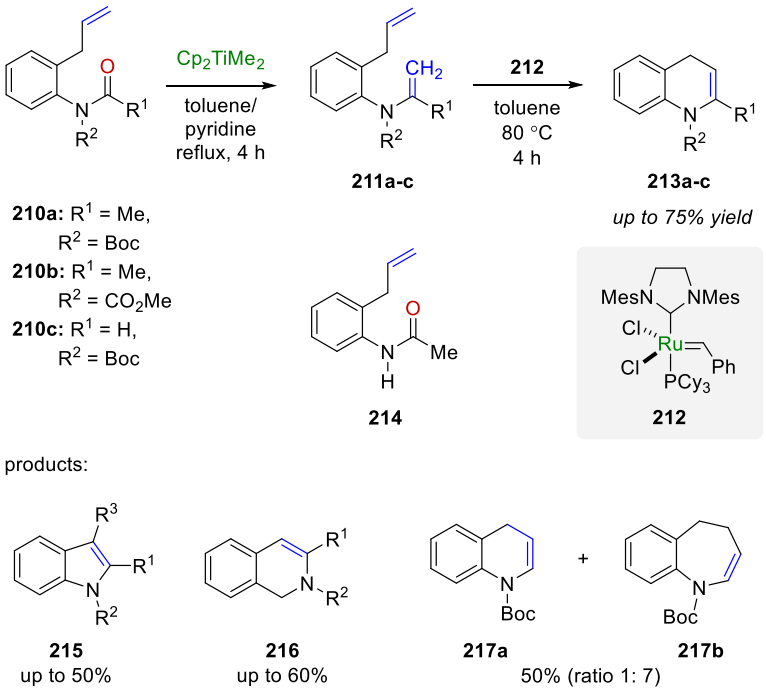
The use of strategy II with metal alkylidenes for the formation of cycloalkenes and cyclic enol ethers was further exploited by Allwein and Rainier in 1998 with an application to the synthesis of a family of compounds associated with neurotoxicity, "red tide" catastrophes, and potent antimicrobial activity.[65] They developed a three-step protocol for the synthesis of fused ether ring systems **198** that included an enol ether epoxidation of **194** to provide **195**, C-C bond formation to form **196**, and finally a ring-closing metathesis of **196** to **197** (Scheme 25). The ring-closing metathesis was performed through pre-functionalization of the carbonyl in olefinic-ester substrate **199** with Takai's conditions,[66] providing primarily the olefinated ester **200** and only trace amounts of ring-closing metathesis product **202**. A stoichiometric amount of Schrock's molybdenum alkylidene catalyst **201** was then employed to perform the ring-closing metathesis in 76% yield.

Scheme 26. Mechanism of the Takai-Utimoto Conditions



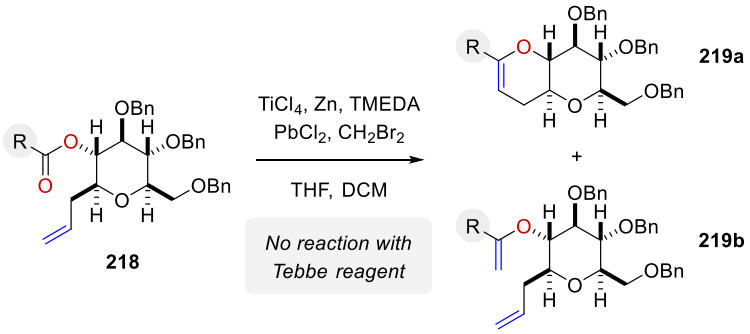
In the following years Takai-Utimoto reaction conditions were developed to realize similar cyclization strategies. Specifically, Takai-Utimoto conditions for a Wittig-type olefination were reported in 1994 that utilized an alkyl halide, PbX_2, $TiCl_4$, and Zn.[66] The reaction begins with the formation of a zinc-carbenoid species **204**, followed by transmetalation with PbX_2 as an accelerant (Scheme 26). Reduction and a second transmetalation lead to geminal dizinc **207**. The formation of titanium-containing geminal dimetallic compound **208a** occurs prior to olefination of carbonyl compound **17**. The Takai and Utimoto group assumed the Tebbe-type complex **208b** as another possible key intermediate for the methylenation of carbonyl compounds. These conditions employed strategy II where initial carbonyl olefination is followed by olefin metathesis.

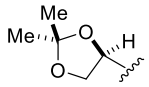
Scheme 27. Synthetic Route to Benzo-Fused *N*-heterocycles by Bennasar



Bennasar and co-workers[67] employed strategy II for the synthesis of 1,4-dihydroquinolines using the Petasis reagent.[58] Methylenation of *N*-protected olefinic amides following a ruthenium-catalyzed ring-closing metathesis of the resulting enamides allowed for the formation of 1,4-dihydroquinolines **213a-c** in up to 75% yield (Scheme 27). Acetanilide **214** was obtained in only 20% yield after treatment with dimethyl titanocene, presumably as a consequence of its competitive interaction with the amide and carbamate carbonyl groups. Enamides **210a** and **210b** underwent olefin metathesis reaction with the second-generation Grubbs catalyst **212**, also in 75% yield, showing that the steric hindrance of the protecting group does not affect the reactivity of the catalyst. The Bennasar group also transformed the hydroquinolines obtained into quinolines. One year later, the Bennasar group expanded this protocol to the syntheses of indoles **215**, 1,2-dihydroisoquinolines **217a**, and dihydrobenzoazepines **217b**.[68] In general, the synthesis of dihydrobenzoazepines resulted in lower yields and mixture of products due to alkene isomerization reactions during the ring-closing metathesis step. An exception was **217a** and **217b**, where the addition of benzoquinone to the reaction mixture reduced the isomerization process and increased the yield to 50%.

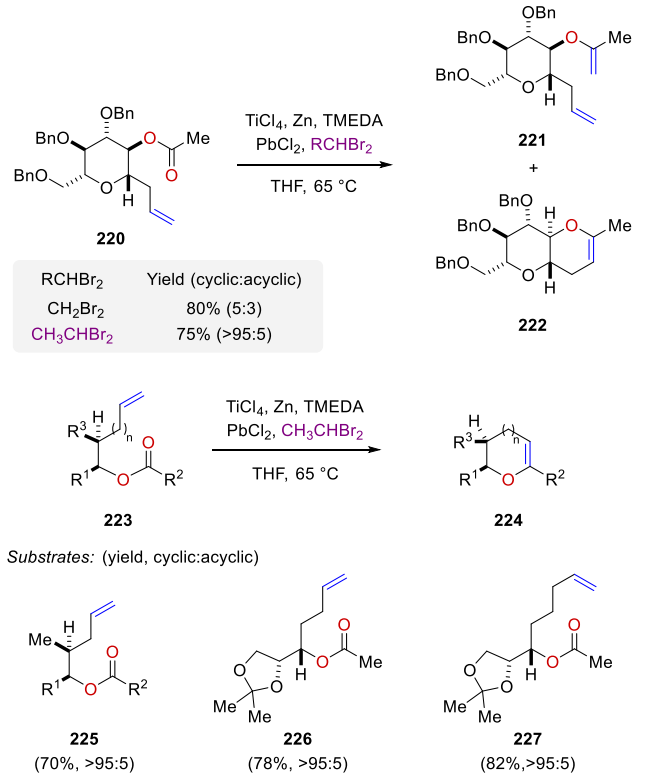
Scheme 28. Modified Takai-Utimoto Reduced Titanium Reagent for the Olefinic Ester Cyclization by Rainier



entry	R =	yield (%)	ratio **219a** : **219b**
1	Me	80	5:3
2	*i*Pr	88	2.4:1
3		71	>95:5
			a:b dependent on ester sterics

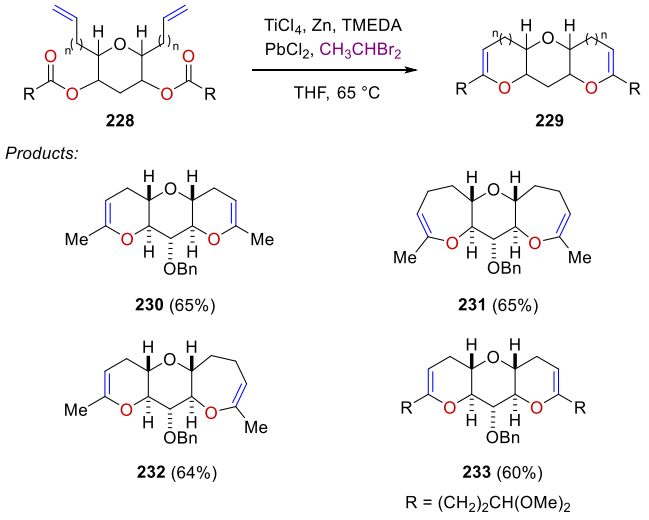
Majumder and Rainier were able to further optimize the metathesis reaction[69] using the Takai-Utimoto titanium alkylidene[66] to achieve the preferential formation of the cyclic enol ether product **219a** over the acyclic enol ether product **219b** (Scheme 28). Initial investigations using the Takai-Utimoto alkylidene demonstrated the mild nature of the protocol and additionally determined that unlike Nicolaou's report,[64] in which cyclic enol ethers resulted from acyclic enol ether intermediates and a subsequent enol ether ring-closing metathesis, the acyclic enol ethers were not precursors to cyclic enol ethers. Therefore, a Strategy I reaction mechanism was proposed wherein an olefin metathesis reaction occurred followed by a carbonyl olefination reaction forming the cyclic enol ether metathesis product. It was determined that these metathesis reactions utilizing the Takai-Utimoto reagent protocol were dependent on the steric environment of both the ester and olefin moieties.

Scheme 29. Reactivity of Reduced Titanium Alkylidenes for Cyclic Enol Ether Formation by Rainier and Iyer



Iyer and Rainier later discovered that the specific type of *in situ* generated titanium alkylidene reagent was crucial to the ratio of acyclic to cyclic enol ether metathesis products (**221** and **222**, Scheme 29).[70] The titanium methylidene reagent derived from dibromomethane as the alkylidene source favored the formation of the acyclic enol ether product, while the corresponding ethylidene reagent resulting from dibromoethane produced the cyclic enol ether as the sole metathesis product. Further exploration into the substrate scope with this updated protocol determined that the ratio of products greatly favored or provided solely the cyclic enol ether metathesis product **224** in up to 82% yield.

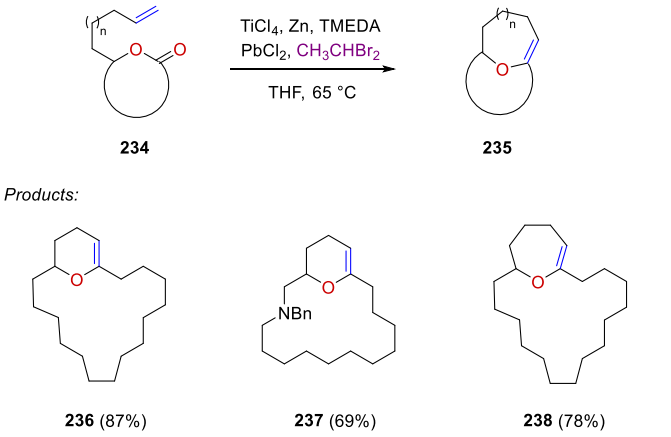
Scheme 30. Polycyclic Ether Skeletons Synthesis by Rainier



In 2009, the application of reduced titanium ethylidene reagents was reported for the rapid entry into polycyclic ether skeletons common in the brevetoxin class of compounds.[71] This two-directional approach allowed for the formation of tricyclic ether rings

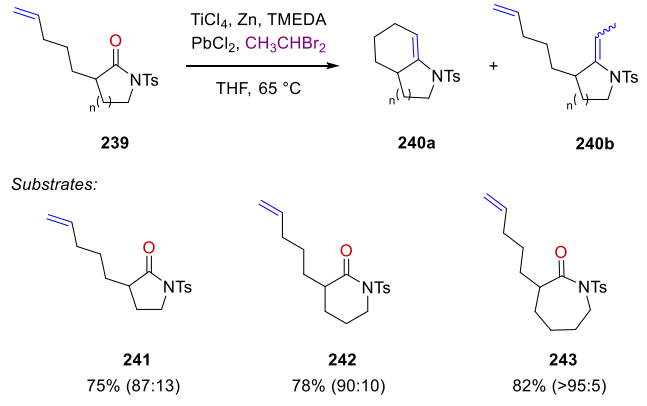
via the ring-closing metathesis reaction of substrates containing two olefin ester moieties. The optimized reaction conditions provide 6- and 7-membered cyclic enol ethers and could perform the double metathesis reaction in up to 65% yield (**230-233**, Scheme 30). The use of this carbonyl-olefin metathesis strategy for the synthesis of cyclic enol ethers allowed for the formation of a heptacyclic compound from *C*-glycoside precursor in just six steps.

Scheme 31. Olefinic Lactone Cyclization by Rainier



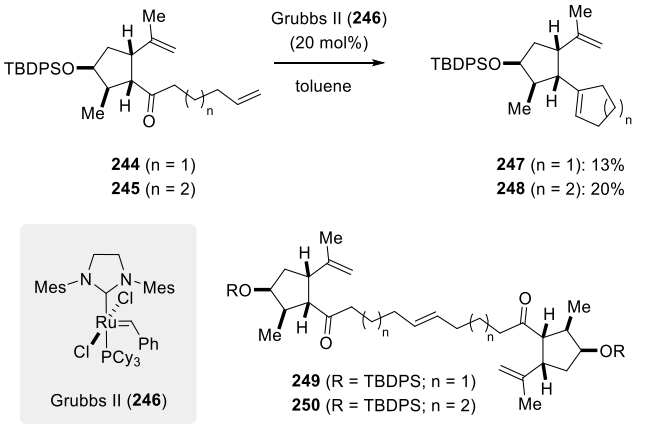
Following their success with the carbonyl-olefin metathesis reaction to form cyclic enol ethers, the Rainier group reported a similar application to the synthesis of macrocycles.[72] Macrocyclic motifs, as shown in Scheme 31, are present in a number of biologically active small molecules[73] and general synthetic protocols for their formation are desirable. Rainier was able to apply the previously reported conditions[70] relying on the use of dibromoethane to access macrocyclic ethers in excellent yields. Specifically, 6- and 7-membered cyclic enol ethers **236-238** were formed within the structure of macrocyclic compounds in up to 87% yield.

Scheme 32. Synthesis of Cyclic Enamides by Rainier



Lastly, Zhou and Rainier were able to further exploit this reduced, *in situ* generated titanium ethylidene reagent for the formation of cyclic enamides[74] from olefinic-amide and olefinic-lactam substrates in good yield and high selectivity towards the cyclic enamide (Scheme 32). 5-, 6- and 7-membered lactams (**241-243**) provided 75-82% yield of the carbonyl-olefin metathesis products with greater selectivity for the cyclic product with increased ring size of the lactam.

Scheme 33. Ruthenium Alkylidene-Mediated Carbonyl-Olefin Metathesis as Reported by Chakraborty and Roy



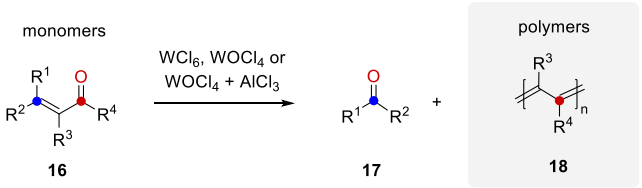
In 2016, Chakraborty and Roy reported a study aimed at the synthesis of cyclopentanes and medium-sized rings relying on a Grubbs II (**246**) catalyzed ring-closing olefin-olefin metathesis sequence and Grubbs II-mediated carbonyl-olefin metathesis.[75] Specifically, terminal alkenes **244** and **245** are converted with 20 mol% Grubbs II (**246**) to result in the formation of cyclopentene **247** and cyclohexene **248** in 13% and 20% yield, respectively, as the carbonyl-olefin metathesis products. Additionally, the formation of the olefin-olefin metathesis product (not shown) is observed in both reactions in up to 40% yield. The authors state that ring-closing carbonyl-olefin metathesis is known to require stoichiometric amounts of Grubbs II (**246**) to proceed, however, carbonyl-olefin metathesis has never been observed with ruthenium alkylidenes and reported examples rely exclusively on stoichiometric amounts of molybdenum alkylidenes as reagents. Based on the ^{1}H-NMR and ^{13}C-NMR spectra obtained by Roy and Chakraborty, we postulate that the products obtained are in fact the dimers **249** and **250** resulting upon cross olefin-olefin metathesis. Spectra included in the original report do not extend to the carbonyl region, which consequently do not allow for differentiation between the carbonyl-olefin metathesis products lacking the carbonyl functionality or the dimeric products formed. It thus appears that compounds **247** and **248** were misassigned and ruthenium-alkylidenes such as **246** do not promote carbonyl-olefin metathesis.

The use of metal alkylidenes, specifically Ti-, Ru-, W-, and Mo-alkylidenes, has been a seminal reaction paradigm for carbonyl-olefin metathesis. Two strategies to utilize these alkylidenes for carbonyl-olefin metathesis have been developed, relying on either an initial olefin metathesis, followed by a carbonyl-olefination (Strategy I) or the reversed approach, employing an initial carbonyl-olefination, followed by olefin metathesis (Strategy II) to access the desired olefin. Both of these strategies have been applied to synthesize a myriad of highly functionalized products including cyclic enol ethers, benzo-fused *N*-heterocycles, and cyclic enamides. Notably, many of these products remain inaccessible with recently developed catalytic protocols for carbonyl-olefin metathesis, which shows the synthetic value of these stoichiometric approaches. Additionally, metal alkylidene-mediated carbonyl-olefin metathesis reactions remain the only strategies currently used in reports of natural product synthesis with the exception of one early example relying on a Paternò-Büchi approach.

4. CARBONYL-OLEFIN METATHESIS POLYMERIZATIONS

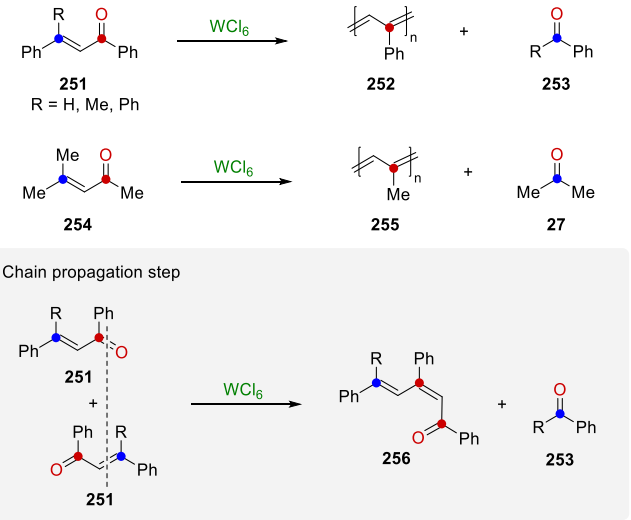
Amongst the earliest reported carbonyl-olefin metathesis reactions were the polymerizations of enones **16** with tungsten-based reagents, resulting in the formation of conjugate polymers **18** (Scheme 34). These types of carbonyl-olefin metathesis reactions were initially referred to as "carbonyl-olefin exchange reactions," and were reported as early as 1983.[14] Although the polymers accessible by this approach are important in various areas of materials science, the transformation remained limited in its scope with only three reported monomers undergoing carbonyl-olefin metathesis. Nevertheless, the reaction holds great synthetic potential and raises interesting mechanistic questions.

Scheme 34. Carbonyl-Olefin Exchange Reactions Enabling Polymerizations



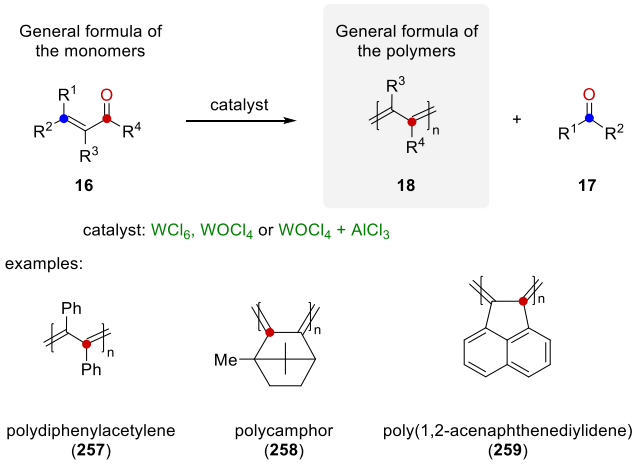
In particular, a consecutive mechanism relying on olefin metathesis, carbonyl-olefin metathesis and final carbonyl metathesis steps was proposed that postulated efficient reactivity of metal-oxo intermediates in subsequent alkene additions. Interestingly, this reactivity has proven elusive in attempts to render metal alkylidene-mediated carbonyl-olefin metathesis reactions catalytic. An additional interesting aspect of carbonyl-olefin metathesis polymerizations is the reliance on tungsten-based reagents to promote the desired transformation, which could exhibit Lewis acid characteristics or form tungsten alkylidenes *in situ*. This chapter summarizes the developments in the area of carbonyl-olefin metathesis polymerizations and focuses on reaction scope, catalyst investigation, optimization of reaction conditions, and mechanistic insights obtained.

Scheme 35. Carbonyl-Olefin Exchange Reaction as Synthetic Route to Polyconjugated Polymers by Schopov



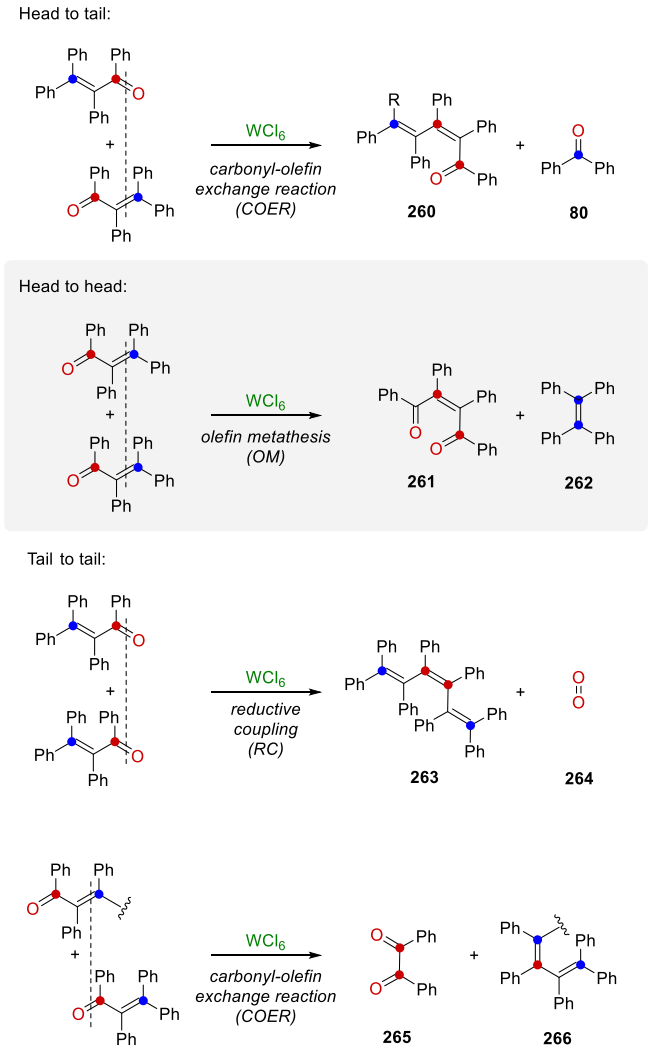
Conjugated polymers are an important part of polymer science, with applications in the fields of bioengineering, materials and biosensors. This class of materials has unique and valuable properties—such as desirable electrical characteristics, conductivity, photoconductivity, paramagnetism, and catalytic activity—that have been extensively investigated.[76] The general methods to prepare conjugated polymers include polymerizations, polycondensation, and polymer analogous conversion.[77] In 1983, Schopov discovered the carbonyl-olefin exchange reaction (COER) as an additional tool for accessing conjugated polymers.[14] Specifically, upon treatment of α,β-unsaturated ketone **251** with WCl_6, polyphenylacetylene **252** and benzaldehyde (**253**, R = H, Scheme 35) were formed. Additionally, polymethylacetylene **255** was also accessible from mesityl oxide **254** and WCl_6.[14,78] Subsequent investigations revealed that substituting the R-group in **251** for a methyl or phenyl group similarly enabled the formation of **252**, and the nature of byproduct **253** affected the yield of the polymer; specifically, benzaldehyde and acetophenone were found to interact with WCl_6, while benzophenone did not react or affect the reactivity, leading to higher yields of **252**.[15] Chain propagation, the first step of COER, is described as double bond cleavage to form a new carbonyl compound **256** and a new C−C double bond in **256**, similar to the redistribution of atoms observed in olefin metathesis reactions.[16] Newly formed dimer **256** contains a carbonyl and olefin end-groups that are able to undergo COER with a second α,β-unsaturated ketone and continue the process to obtain the conjugated polymer. This polymerization is thus considered a stepwise process and a polycondensation reaction.

Scheme 36. General Formulas and Examples of Conjugated Polymers Obtained with Carbonyl-Olefin Exchange Reaction



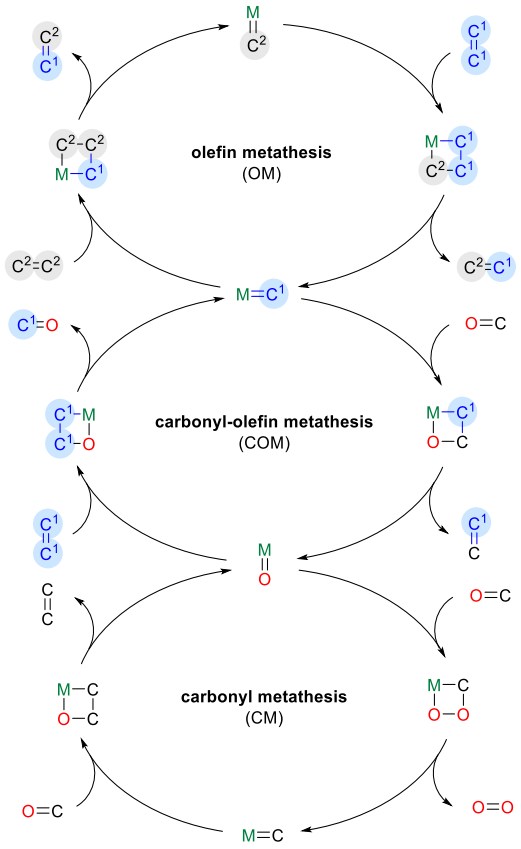
The groups of Schopov and Jossifov carried out several investigations on COER to determine the optimized reaction conditions and important experimental results were obtained: a) the general formula of the monomers is a substituted propenone **16**[14,15,78] (Scheme 36); more substituted monomers lead to higher yields,[18] b) the reaction can be carried out without solvent, or in benzene or chlorobenzene as the optimal solvents,[14,15] c) higher yield and molecular weight were observed when increasing the amount of WCl_6 (up to equimolar ratios), time, and temperature (120 °C), [15,19] d) during the reaction tungsten changes its degree of oxidation,[78] and e) the polymer is obtained as a doped complex with WCl_6 while polymer **18** can be obtained after a treatment with concentrated sodium hydroxide solution.[18] Additionally, it was found that $WOCl_4$ or $WOCl_4$ with $AlCl_3$ as additives led to higher yields of **18** and, in some cases, quantitative transformation of the monomer.[20] Several polyconjugated polymers were obtained under the optimized reaction conditions such as polydiphenylacetylene (**257**),[18] polycamphor (**258**),[79] and poly(1,2-acenaphthenediylidene) (**259**).[14]

Scheme 37. Types of Propagation Steps Proposed by Jossifov



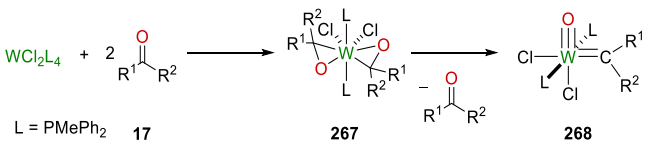
Importantly, several compounds including benzophenone **80**, tetraphenylethylene **262**, traces of molecular oxygen **264**, and dibenzyl **265** were identified as byproducts of this polymerization[21] (Scheme 37). The presence of these compounds supported the hypothesis that several double bond forming reactions were taking place during the polymerization process. Considering the olefin moiety the "head" and the carbonyl group the "tail," three types of propagation steps can occur: COER (considered a head to tail propagation), olefin metathesis (OM, considered a head to head propagation), and reductive coupling (RC, considered a tail to tail propagation). Compound **265** was not observed as part of the byproducts reported and the origin of **266** is probably due to an inner double bond metathesis with a carbonyl group.

Scheme 38. Possible Mechanism for the Synthesis of Polyconjugated Polymers by Schopov and Jossifov



The proposed mechanism for the tungsten-catalyzed polymerization by Schopov[21] and Jossifov[21,80,81] involves all three types of propagation steps, specifically OM, COM (or COER), and RC[82] transformations taking place simultaneously (Scheme 38). The OM involves the formation of metallacyclobutane intermediates from olefins and metal alkylidene complexes *via* [2+2] cycloadditions and subsequent fragmentations. The COM reaction consists of the redistribution of the metal carbene generated from OM and a carbonyl group to form a new olefin and an oxo-metal complex. Then, the oxo-metal species could either react with a second olefin or with a carbonyl through a [2+2] cycloaddition to start the next cycle of CM. This cycle entailed the formation of a dioxometallacyclobutane and subsequent cleavage to the metal carbene and molecular oxygen. The metal carbene could then react with a second carbonyl group to form an olefin and regenerate the oxo-metal complex to continue the cycle. The hypothesis is based on the existence of similar catalytic systems,[83] the established [2+2]-metathesis reactions mechanism relying on transition metal carbene complexes,[84] the byproducts observed, and the tungsten oxo-alkylidene complexes reported by Bryan and Mayer.[85]

Scheme 39. Synthesis of Tungsten Metallaoxirane and Tungsten Oxo-Alkylidene Complexes by Mayer

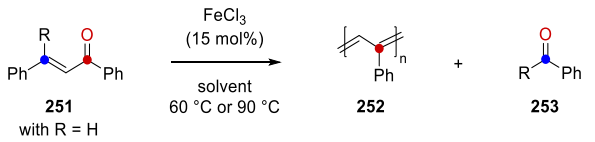


Notably, Bryan and Mayer reported a series of oxo-alkylidene complexes generated *via* oxidative addition of ketones to form two divalent ligands with tungsten (Scheme 39). $WCl_2(PMePh_2)_4$ reacts with two equivalents of ketone forming a metallaoxirane complex **267** *via* substitution of two phosphine ligands. Some of these complexes decomposed to the oxo-alkylidene complex **268** at room temperature in a few days. However, small changes in the ketones affected the reactivity: tetrasubstitutedethylene

compounds, ketones, and other unidentified byproducts were formed together with oxo-tungsten complex ($W(O)Cl_2L_3$). Therefore, this proved not to be a general method for preparing oxo-alkylidene complexes. Based on the past evidence and existing literature, Jossifov investigated the polymer formation *via* reductive coupling of diketone **267** with $WCl_6 \cdot AlCl_3$,[86] which was previously used as a two-component catalyst for COER.[20] Polydiphenylacetylene with carbonyl end-groups was obtained, although molecular oxygen was not detected, which means that the polymerization proceeded as a normal RC. This result supports part of the "carbene mechanism" (Scheme 38).

In particular, a consecutive mechanism relying on olefin metathesis, carbonyl-olefin metathesis and final carbonyl metathesis steps was proposed that postulated efficient reactivity of metal-oxo intermediates in subsequent alkene additions. Interestingly, this reactivity has proven elusive in attempts to render metal alkylidene-mediated carbonyl-olefin metathesis reactions catalytic. An additional interesting aspect of carbonyl-olefin metathesis polymerizations is the reliance on tungsten-based reagents to promote the desired transformation, which could exhibit Lewis acid characteristics or form tungsten alkylidenes *in situ*.

Scheme 40. Synthesis of polyphenylacetylene by iron(III) chloride by Dimova



251 with R = H — **252** — **253**

solvent: 1,2-dichloroethane (60 °C) 76%
toluene (90 °C) 81%

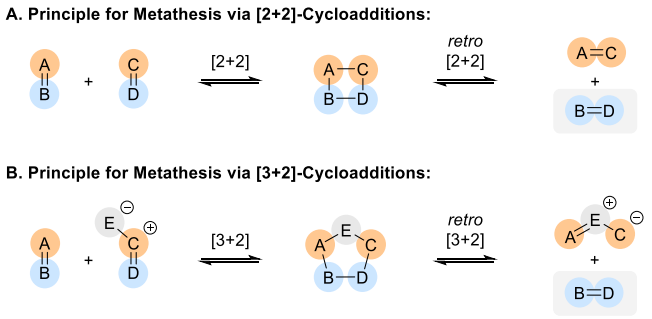
In 2018, Dimova and coworkers reported an $FeCl_3$-catalyzed carbonyl-olefin metathesis polymerization reaction of chalcone **251** to form polyphenylacetylene **252**.[87] Specifically, when chalcone **251** is converted with 15 mol% $FeCl_3$ at 60 °C in 1,2-dichloroethane, the authors observe the formation of polyphenylacetylene **252** in 76% yield as a predominantly trimeric product. In comparison, when the reaction is conducted in toluene at 90 °C under otherwise identical reaction conditions, **252** is obtained in increased yields of 81% while fractions of molecular masses up to 5000 $g \cdot mol^{-1}$ are registered.

In summary, these examples highlight the potential of carbonyl-olefin metathesis as a tool for the polymerization of enones. Initial mechanistic studies suggest that all three types of propagation occur simultaneously in these transformations to form the desired polymer products. Despite the fact that the polymers synthesized by these transformations are limited in scope and size, the reactions hold tremendous synthetic potential. While new advances have been reported recently for other categories of carbonyl-olefin metathesis, the most recent developments in tungsten-mediated carbonyl-olefin metathesis polymerizations date back to the 1990s. Only a single, more recent report describes the use of Lewis acids for carbonyl-olefin metathesis polymerization reactions.

5. ORGANOCATALYTIC CARBONYL–OLEFIN METATHESIS REACTIONS

The first catalytic strategy for carbonyl-olefin metathesis was reported by Lambert and coworkers in 2012.[88] In contrast to the classic [2+2]-cycloaddition and retro-[2+2]-cycloaddition paradigm usually operative in double bond metathesis reactions, their reaction design principle takes advantage of a [3+2]-cycloaddition and retro-[3+2]-cycloaddition using 1,3-dipoles (Scheme 41). The reliance on this alternative class of pericyclic reactions circumvents some of the challenges presented by [2+2] manifolds; however, 1,3-dipolar cycloadditions present their own set of unique issues. Principle amongst these challenges is the typically high stability of the intermediate, five-membered ring cycloadducts. In contrast to the four-membered ring intermediates of both olefin metathesis and carbonyl-olefin metathesis reactions involving oxetanes, the Lambert design requires some means to destabilize the intermediate cycloadducts, whether it is through the use of strained substrates or, ideally, catalyst design.

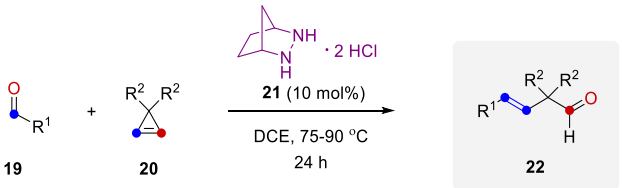
Scheme 41. Reaction Design Principle for the First Catalytic Carbonyl-Olefin Metathesis Reaction.



The specifics of the Lambert blueprint call for the use of hydrazine catalysts, which engage the carbonyl component by condensation to form azomethine imines (or more accurately, their conjugate acid hydrazonium ions). The metathesis then proceeds by reversible 1,3-dipolar cycloadditions with the olefin. The key principle in this design is that, by virtue of the locally symmetric nature of the pyrazolidine intermediate, cycloreversion can occur *via* two different exit channels: one to reform the starting materials and the other to generate new olefin and hydrazonium intermediates. In precisely the same way as olefin metathesis reactions, the equilibrium point of this inherently reversible process is dictated by elements of ring strain, conjugation, or mass action. It should be stressed that a particular advantage of this platform is that the engagement of the carbonyl and olefin occurs through mechanistic processes—condensation and cycloaddition, respectively—that are compatible with a broad range of functionality. This design thus holds promise for substantial generality, even if much of that promise is as yet unrealized. Nevertheless, this reaction paradigm has been shown to be applicable to catalytic ring-opening and ring-closing carbonyl-olefin metathesis reactions with several distinct substrate architectures.

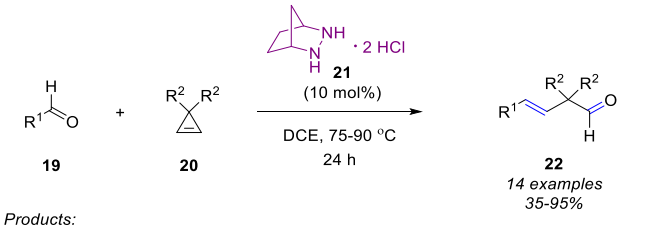
5.1 Ring-Opening Carbonyl-Olefin Metathesis

Scheme 42. Catalytic Ring-Opening Carbonyl-Olefin Metathesis *via* 1,3-Dipolar Cycloadditions.

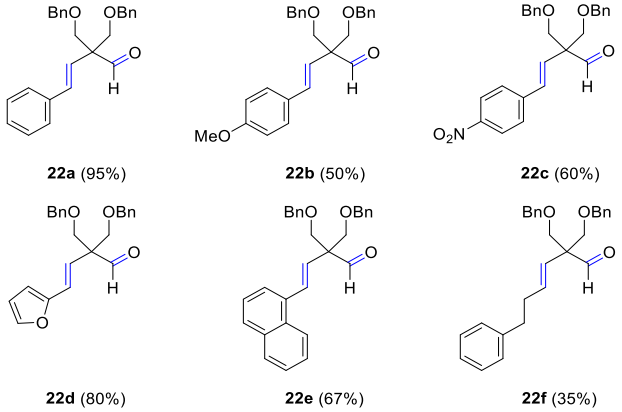


In the first implementation of the hydrazine-catalyzed design, Griffith, Vanos, and Lambert[88] demonstrated the ring-opening carbonyl-olefin metathesis (ROCOM) of cyclopropenes in 2012 (Scheme 42). The optimal catalyst for this transformation was the symmetric bicyclic hydrazine **21** as its bis-hydrochloride salt. With catalytic **21**, aryl or aliphatic aldehydes **19** underwent ROCOM with cyclopropenes **20** to furnish β,γ-unsaturated aldehydes **22**. Notably, the carbonyl-olefin metathesis products were formed with complete (*E*)-selectivity.

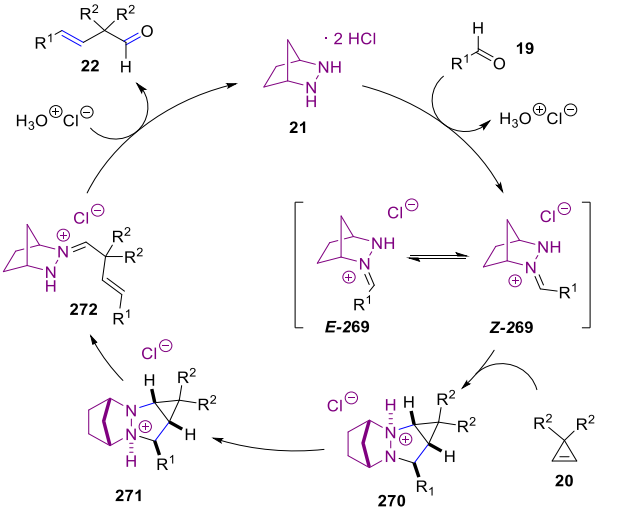
Scheme 43. Hydrazine-Catalyzed Ring-Opening Carbonyl–Olefin Metathesis by Lambert.



Products:



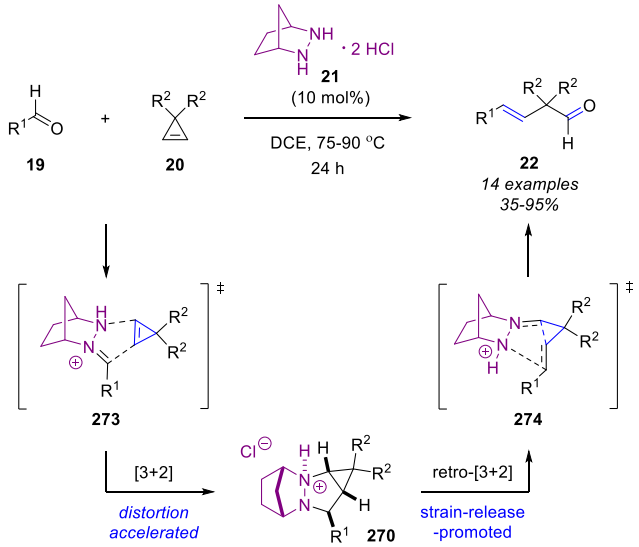
Mechanistic Hypothesis:



These reactions were found to proceed in up to 95% yield for a variety of electronically differentiated aryl aldehydes including furan and thiophene derivatives. Aliphatic aldehydes proceed in yields of 35% with the use a slow addition protocol (Scheme 43). It was presumed that the lower efficiency of the aliphatic substrates was due at least in part to side reactions resulting from deprotonation/tautomerization of the intermediate hydrazonium intermediates. The proposed mechanistic hypothesis involves initial condensation between aldehydes **19** and the symmetric hydrazine catalyst to form the corresponding hydrazonium ion **269**. Interestingly, of the two possible geometric isomers of this hydrazonium ion (***E*-269** and ***Z*-269**), the authors propose (and calculations support) that cycloaddition with cyclopropane **20** is favored for ***E*-269** *via* an *exo*-transition state due to minimized steric interactions, despite the fact that ***Z*-269** is the thermodynamically favored isomer. The resulting pyrazolidine cycloadduct **270** undergoes proton transfer to form **271**, which then proceeds through strain-relieving cycloreversion to result in hydrazonium

ion **272**. Hydrolysis of **272** reveals the carbonyl-olefin metathesis product, enal **22**, with concomitant regeneration of the hydrazine catalyst **21**.

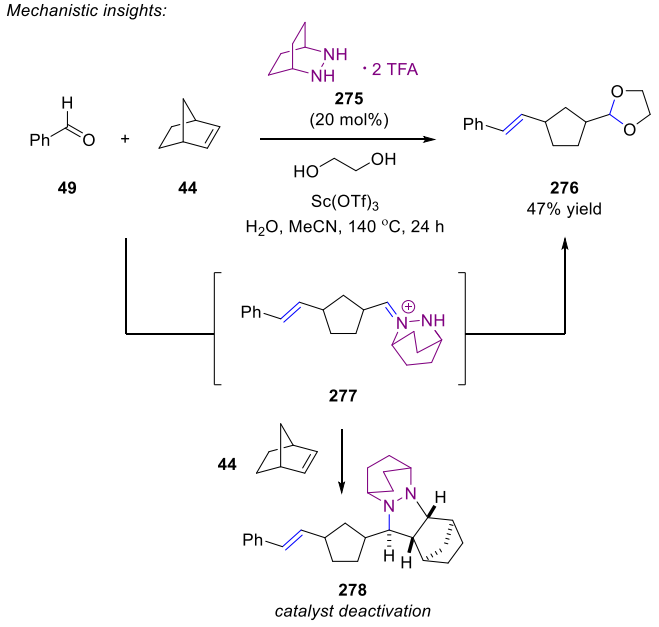
Scheme 44. Distortion-Accelerated and Strain-Release-Promoted [3+2] and retro-[3+2] in Organocatalytic Carbonyl-Olefin Metathesis by Lambert and Houk.



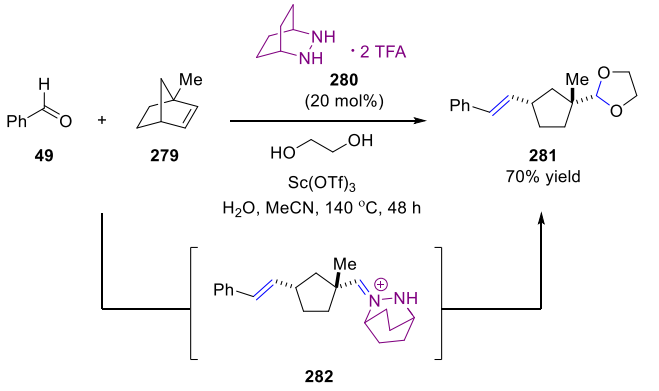
The Lambert and Houk groups[89] followed up this initial report with a detailed mechanistic investigation of this hydrazine-catalyzed carbonyl-olefin metathesis reaction platform.[88] Computational analysis fully supported the mechanistic rationale described above and underscored the role of ring strain of the cyclopropane substrates (**20**). Specifically, the substantial cyclopropane ring strain accelerated the initial [3+2] cycloaddition and led to intermediate fused cyclopropane cycloadducts that also benefited from high ring strain to accelerate the [3+2]-cycloreversion step (Scheme 44). Of particular importance was the finding that other strained olefins such as cyclobutenes and cyclopentenes were likely to have significantly higher activation barriers for the key cycloreversion step using hydrazine catalyst **21**. This understanding argued strongly for the design of alternative hydrazine structures that could induce more facile cycloreversions with less reliance on substrate ring strain.

Scheme 45. Hydrazine-Catalyzed Ring-Opening Carbonyl-Olefin Metathesis of Norbornenes by Lambert.

Mechanistic insights:



Catalytic ring-opening carbonyl-olefin metathesis of 1-methylnorbornene



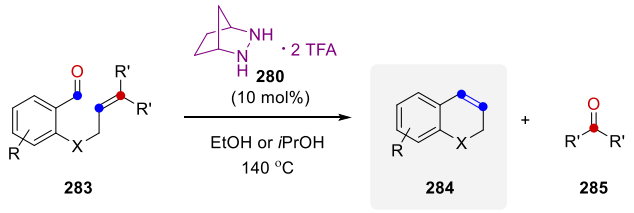
In 2020, Lambert and coworkers expanded the concept of hydrazine-catalyzed ring-opening carbonyl-olefin metathesis reactions of aldehydes to include norbornenes (Scheme 45), using a combined approach of catalyst design and computational analysis.[90] The major challenge confronting a shift to a significantly less-strained substrate like norbornene is that the [3+2]-cycloreversion becomes both endergonic and the rate-determining step of the catalytic cycle. In order to identify a hydrazine that would enable a viable catalytic process with such substrates, a virtual screen of catalysts was conducted. Each step of the catalytic cycle was calculated in order to avoid misleading winners (i.e. structures that minimized cycloreversion but at the expense of an energetically inaccessible other step), and indeed a number of important potential pitfalls were identified. From this expansive study, a second-generation [2.2.2]-bicyclic hydrazine catalyst was identified that promised reasonably accessible cycloaddition and cycloreversion energies with norbornene.

Both of the cycloaddition and cycloreversion steps between benzaldehyde (**49**) and norbornene (**44**) with the [2.2.2]-bicyclic hydrazine **275** (Scheme 45) could be investigated separately because of the isolable nature of the intermediate cycloadducts. These studies confirmed the computational predictions and suggested a catalytic process should be attainable. Initial results proved encouraging as the use of 20 mol% **275** resulted in the formation of acetal **276** as the ring-opening metathesis product in 47% yield. However, the formation of cycloadduct **278**, resulting from cycloaddition of hydrazonium intermediate **277** with a second

equivalent of norbornene **44**, was also observed. As **278** was resistant to cycloreversion under the reaction conditions, its formation resulted in full catalyst deactivation. Based on these results, it was postulated that hydrolysis of **277** is a key step in the turn-over of the hydrazine catalyst **275**. In an attempt to overcome this limitation, methylnorbornene **279** was utilized to destabilize hydrazonium **282** by the introduction of steric strain and hopefully facilitating hydrolysis compared to undesired cycloaddition of a second equivalent of norbornene **279**. In fact, the reaction between **49** and **279** provided 74% yield of **281**, demonstrating the feasibility of ring-opening carbonyl-olefin metathesis of norbornenes. The authors conclude that competitive cycloaddition of hydrazonium **282** is still observed even with methylnorbornene **279**, and thus future efforts should focus on the development of catalysts that promote a more facile hydrolysis step.

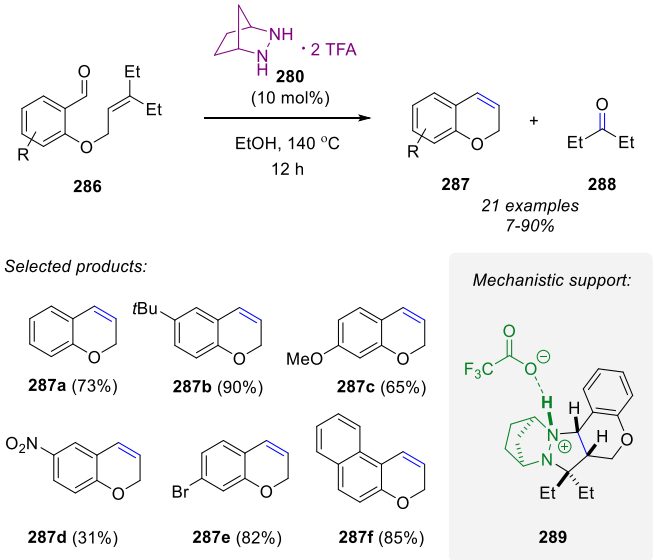
5.2 Ring-Closing Carbonyl-Olefin Metathesis

Scheme 46. Catalytic Ring-Closing Carbonyl-Olefin Metathesis *via* 1,3-Dipolar Cycloadditions.



In 2019, Lambert and coworkers extended hydrazine-catalyzed carbonyl-olefin metathesis to the arena of ring-closing metathesis reactions (Scheme 46). Similar to the reaction design for ring-opening metathesis, these transformations rely on the initial condensation between the carbonyl moiety in **283** and the hydrazine catalyst **280** to form a hydrazonium intermediate. This reactive intermediate can then undergo a cycloaddition with the pendant alkene to form the pyrazolidine cycloadduct, which upon retro-[3+2]-cycloaddition and hydrolysis, gives rise to the desired metathesis product **284** and a carbonyl byproduct **285**.

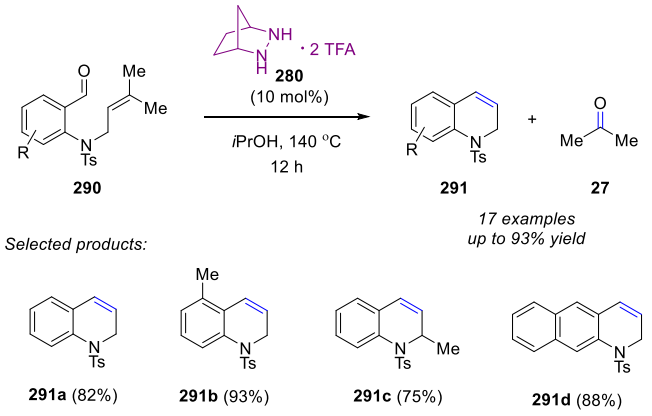
Scheme 47. Synthesis of 2*H*-Chromenes *via* Hydrazine-Catalyzed Carbonyl–Olefin Metathesis by Lambert



Hydrazine-catalyzed carbonyl-olefin metathesis ring-closing reactions were first established by Lambert and coworkers for salicylaldehyde allylic ethers **286** resulting in the formation of *2H*-chromenes **287** (Scheme 47).[91] The method utilizes the [2.2.1]-bicyclic hydrazine **280** as the catalyst and showcases a new approach to afford electronically and functionally differentiated 2*H*-chromenes (**287a-287f**) in up to 90% yield. Interestingly, the corresponding ketone substrates also prove reactive under the optimal reaction conditions; however, the low yields observed with these substrates point to complications in the condensation and/or

cycloaddition steps due to steric strain. Lambert and co-workers were also able to provide additional mechanistic support for the hypothesis of sequential [3+2]- and retro-[3+2]-cycloadditions[88-90] with the crystallization of cycloadduct **289**. The configuration of **289** was confirmed by X-ray crystallographic analysis. The syn-pentane interaction between the gem-diethyl group was speculated to exert steric pressure on pyrazolidine cycloadduct, potentially accelerating the rate of cycloreversion and suppressing deallylative side reaction. Subsequent exposure of **289** to the optimized reaction conditions resulted in the formation of the desired carbonyl-olefin metathesis product **278a** in 73% yield. As opposed to ring-opening metathesis (*vide supra*), the instability of the ketone hydrazonium byproduct allowed rapid hydrolysis, enabling catalyst turnover and minimizing deactivation.

Scheme 48. Synthesis of 1,2-Dihydroquinolines *via* Hydrazine-Catalyzed Carbonyl–Olefin Metathesis by Lambert



In 2020 Lambert and coworkers further expanded the application of hydrazine-catalyzed carbonyl-olefin ring-closing metathesis reactions to the synthesis of 1,2-dihydroquinolines.[92] While the electron donating nitrogen was found to retard the rate of cycloaddition in *N*-allyl-2-aminobenzaldehyde compared to the salicylaldehyde counterpart, it facilitated a more rapid rate-determining cycloreversion. Such rate enhancement permitted the replacement of the diethylallyl group for a less hindered (and commercially available) prenyl group, while still inhibiting any deallylation side reaction. *N*-prenylated aminobenzaldehydes **290** underwent the desired transformation to result in a variety of 1,2-dihydroquinolines **291** bearing distinct substitution in up to 93% yield (Scheme 48). Notably, the corresponding *N*-Boc protected substrates underwent facile *in situ* deprotection to give rise to quinolones in 61% yield.

The use of strained hydrazines as catalysts has served as a powerful reaction design to develop catalytic carbonyl-olefin metathesis reactions. The unique [3+2]-cycloaddition strategy relying on the formation of cyclic hydrazonium intermediates enables ring-opening and ring-closing carbonyl-olefin metathesis reactions that allow for the facile synthesis of acyclic unsaturated aldehydes, chromenes, and dihydroquinolines as highly-desired heterocyclic scaffolds. Mechanistic investigations prompted strategic catalyst design to expand the scope of hydrazine-catalyzed carbonyl-olefin metathesis reaction. While the products obtained following ring-closing carbonyl-olefin metathesis protocols are similarly accessible in Lewis acid-catalyzed approaches, the unsaturated aldehydes resulting upon ring-opening carbonyl-olefin metathesis reactions are not, which renders this a particularly powerful and complementary transformation.

6. LEWIS ACID-CATALYZED CARBONYL-OLEFIN METATHESIS REACTIONS

6.1 Lewis Acid-Mediated Carbonyl-Olefin Metathesis

6.2 Catalytic Carbonyl-Olefin Ring-Closing Metathesis of Aryl Ketones

6.2.1 Formation of 5-Membered Rings

6.2.2 Formation of 6-Membered Rings

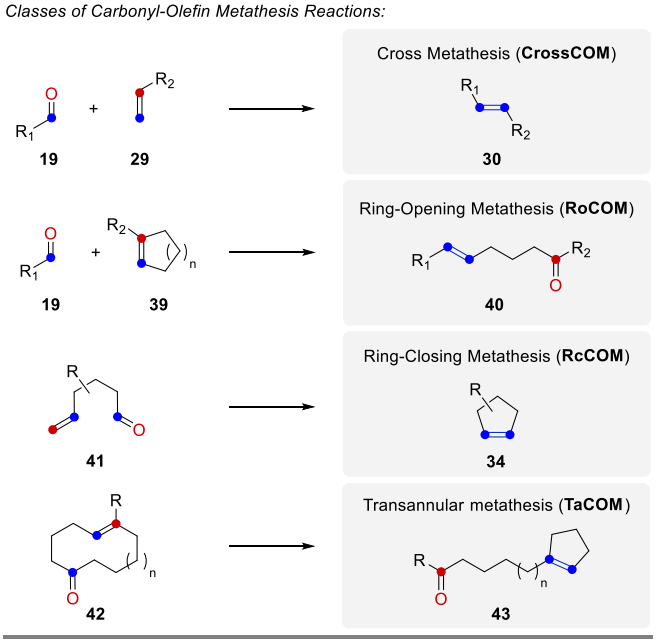
6.3 Catalytic Carbonyl-Olefin Ring-Closing Metathesis of Aliphatic Ketones

6.4 Catalytic Cross-Carbonyl-Olefin Metathesis

6.5 Catalytic Carbonyl-Olefin Ring-Opening Metathesis

6.6 Catalytic Transannular Carbonyl-Olefin Metathesis

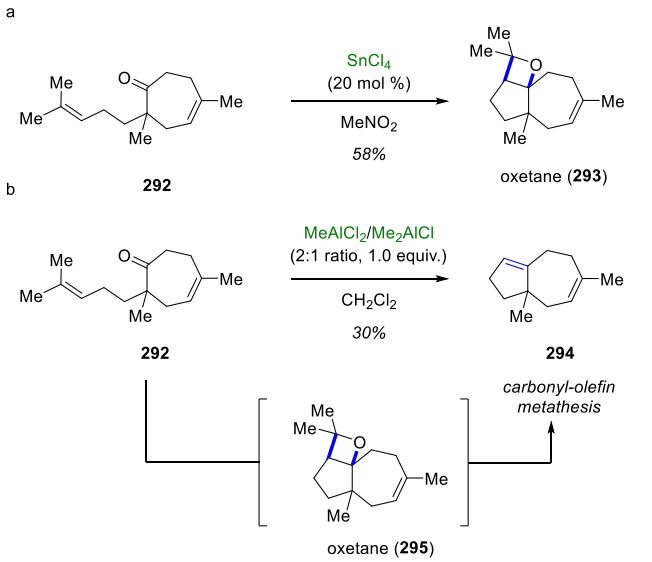
Scheme 49. Lewis Acid-Catalyzed Carbonyl-Olefin Metathesis



In the early 1970s, the first reports appeared of carbonyl-olefin metathesis reactions between carbonyls and alkenes relying on equimolar amounts of Lewis acids. These transformations also proceed *via* initial [2+2]-cycloadditions between the alkene **1** and carbonyl **6** moieties to form intermediate oxetanes **8** (Figure 2A). However in comparison to previous stepwise protocols relying on Paternò-Büchi reactions and thus photochemical irradiation, Lewis acid-mediated approaches undergo *in situ* oxetane formation and fragmentation to provide the desired carbonyl-olefin metathesis products **4** and carbonyl byproducts **7** (Figure 2A). These transformations allow for broader applications and additional substrate complexity while proceeding under overall milder reaction conditions compared to originally reported carbonyl-olefin metathesis conditions based on oxetane pyrolysis.[26,27] The Lewis acid takes on a dual role in these reactions to first activate the carbonyl substrate for a [2+2]-cycloaddition and subsequently the oxetane intermediate formed for a [2+2]-cycloreversion. Importantly, this reaction design principle relies on coordinative interactions between catalyst and substrate to forego the formation of metal-oxygen bonds and thus the formation of the corresponding oxidized metal-oxo species compared to metal alkylidene-mediated carbonyl-olefin metathesis approaches. Consequently, this design principle holds great potential as a catalytic strategy for carbonyl-olefin metathesis and has led to important advances in catalytic ring-closing, ring-opening, transannular and cross metathesis of alkenes and carbonyls (Scheme 49). This chapter provides an overview of carbonyl-olefin metathesis reactions initially mediated by Lewis acids, followed by a detailed discussion of currently available Lewis acid-catalyzed variants for each class of carbonyl-olefin metathesis reactions.

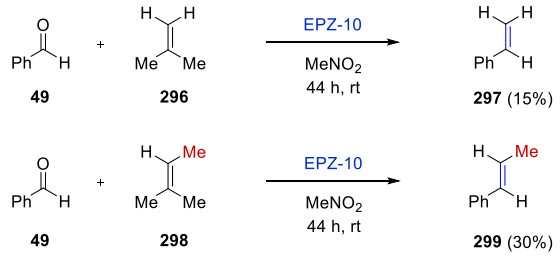
6.1. Lewis acid-Mediated Carbonyl-Olefin Metathesis

Scheme 50. Lewis acid-mediated metathesis reactions by Demole and Snider.

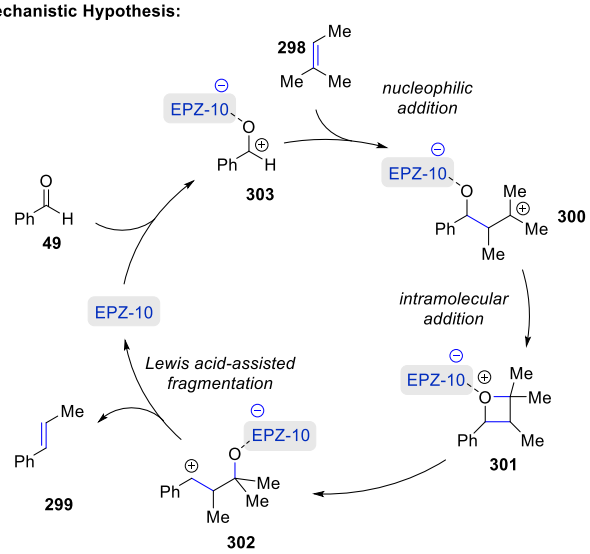


In their studies towards carbon sesquiterpenes, Demole, Enggist and Borer were the first to realize the potential of a one-pot procedure for oxetanes formation relying on Lewis acids. Specifically, *cis*-oxetane **293** was formed and isolated in 58% yield upon subjection of ketone **292** to 20 mol% $SnCl_4$ *via* an intramolecular [2+2]-cycloaddition (Scheme 50a).[93] Following this report, in 1984 Snider employed the use of the same substrate **292** in his studies of intramolecular ene reactions.[94] The treatment of cycloheptanone **292** with stoichiometric amounts of a mixture of $MeAlCl_2/Me_2AlCl$ in a 2:1 ratio provided the formation of metathesis product **294** in 30% yield (Scheme 50b). Snider proposed that the metathesis reaction proceeds through a stepwise cycloaddition to form oxetane **295** *in situ* followed by a retro-cycloaddition to provide the metathesis product **294** upon the loss of acetone. Interestingly, the reaction does not occur in the presence of $Me_{1.5}AlCl_{1.5}$, but a complex mixture is recovered when **292** is treated with stoichiometric amounts of $MeAlCl_2$ indicating the significance of the strength of the Lewis acid in facilitating the carbonyl-olefin metathesis reaction.

Scheme 51. Solid Promoted Lewis Acid-Promoted Carbonyl-Olefin Metathesis by Bickelhaupt and Coworkers

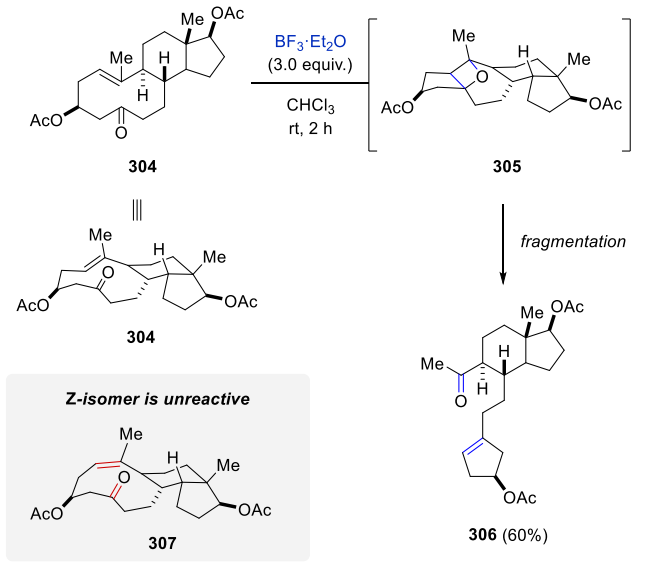


Mechanistic Hypothesis:



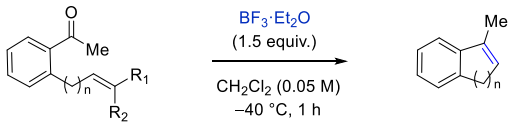
In 1994, the cross carbonyl-olefin metathesis reaction of benzaldehyde **49** and isobutylene **296** or methyl-2-butene **298** was reported by Bickelhaupt, van Schaik, and Vijn[95] to provide yields of 15% and 30%, respectively, of metathesis products **297** and **299** (Scheme 51). A heterogeneous Lewis acid catalyst, EPZ-10,[96] consisting of clay-supported $ZnCl_2$ (12% $ZnCl_2$ content) was used to promote metathesis in this reaction. Interestingly, higher temperatures and reactions times increased conversions but with accompanying byproduct formation. A stepwise mechanism is proposed (Scheme 51) that begins with Lewis acid activation of carbonyl **49**, followed by nucleophilic addition of olefin **298** to form carbocation **300**. An intramolecular addition results in the formation of oxetane **301** which, upon subsequent Lewis acid-assisted fragmentation, yields the carbonyl-olefin metathesis product **299**. The reaction is reported to be limited to carbonyl compounds that lack α-hydrogen substituents due to resulting competing aldol condensation reactions with the acetone byproduct of the carbonyl-olefin metathesis reaction.

Scheme 52. Lewis Acid-Promoted Transannular Carbonyl-Olefin Metathesis by Khripach and Coworkers

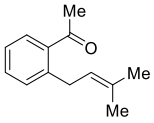
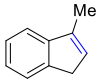
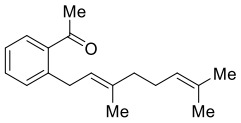
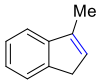
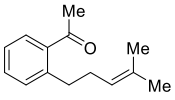


A more complex example of carbonyl-olefin metathesis was reported by Khripach and coworkers in 2006 during their studies towards the synthesis of steroid frameworks.[97] Specifically, carbonyl-olefin metathesis product **306** was produced in 60% yield following attempts by Khripach to protect the carbonyl moiety in seco-steroid **304** as a dithioketal upon treatment with excess $BF_3 \cdot OEt_2$ (Scheme 52). Interestingly, the corresponding Z-olefin isomer **307** failed to undergo the carbonyl-olefin metathesis reaction under identical reaction conditions. The suggested mechanistic hypothesis for this transformation includes an intramolecular, Lewis acid-assisted [2+2]-cycloaddition and cycloreversion of the resulting intermediate oxetane **305**.

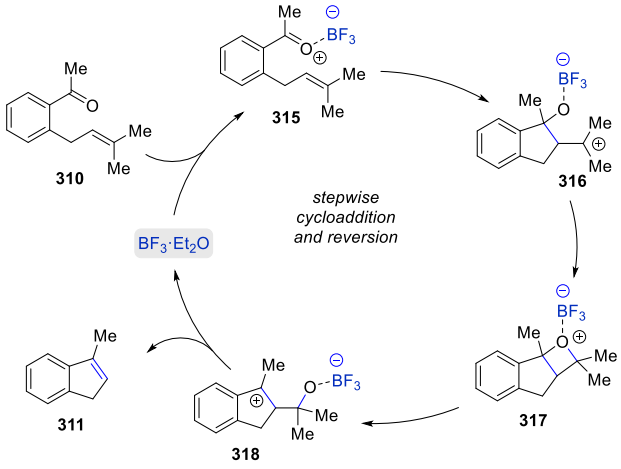
Scheme 53. $BF_3 \cdot OEt_2$ Induced Metathesis Cyclization of Pestalone Derivatives by Schmalz and Coworkers



308 **309**

entry	substrate	product	yield (%)
1	 **310**	 **311**	87
2	 **312**	 **311**	38
3	 **313**	 **314**	75

Mechanistic Hypothesis:



In their work towards marine natural product pestalone, Schmalz and coworkers attempted to deprotonate the ether subunits in *ortho*-prenylated benzophenone and instead detected the formation of an indene-derived metathesis product in 20% yield.[98] Subsequent optimization efforts provided 87% yield for the resulting carbonyl-olefin metathesis products with the optimal conditions requiring 1.5 equivalents of $BF_3{\cdot}OEt_2$ in DCM at −40 °C after one hour (Scheme 53). Further application of this protocol was investigated for a series of acetophenone derivatives. Specifically, substrates bearing prenyl (**310**), geranyl (**312**) and homoprenyl substituents (**313**) in the *ortho* position provided 38-87% yield of the desired carbonyl-olefin metathesis products containing 5- and 6-membered cycloalkenes (**311** and **314**, Scheme 53). The authors propose a stepwise mechanism for this transformation that relies on initial *exo*-trig cyclization of **315** following Lewis acid activation of the carbonyl moiety (Scheme 53). Tertiary carbocation **316** is then formed and isomerizes to the more stable benzylic carbocation **317** *via* an intermediate oxetane.

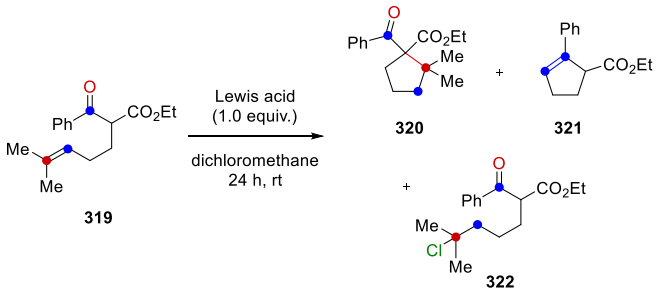
Lastly, fragmentation of carbocation **318** results in the formation of indene **311** as the desired carbonyl-olefin metathesis product with acetone as the byproduct.

6.2. Catalytic Carbonyl-Olefin Ring-Closing Metathesis of Aryl Ketones

Despite the fact that acid-mediated carbonyl-olefin metathesis reactions have been reported in the literature over the last 40 years, acid-catalyzed carbonyl-olefin metathesis reactions have only recently been realized. Lewis acids have now been employed allowing for a catalytic pathway as they activate the carbonyl moiety making it more electrophilic for the nucleophilic attack of the olefin moiety. The coordinating nature of Lewis acids allows for catalyst turnover to occur whereas loss of H^+ of Brønsted acids or metal-oxo species in metal alkylidene promoted metathesis reactions, did not allow for this turnover. This section outlines the application of Lewis acids[26,27,99-102] towards catalytic carbonyl-olefin ring-closing metathesis reactions relying on aryl ketone substrates.

6.2.1 Formation of 5-Membered Rings

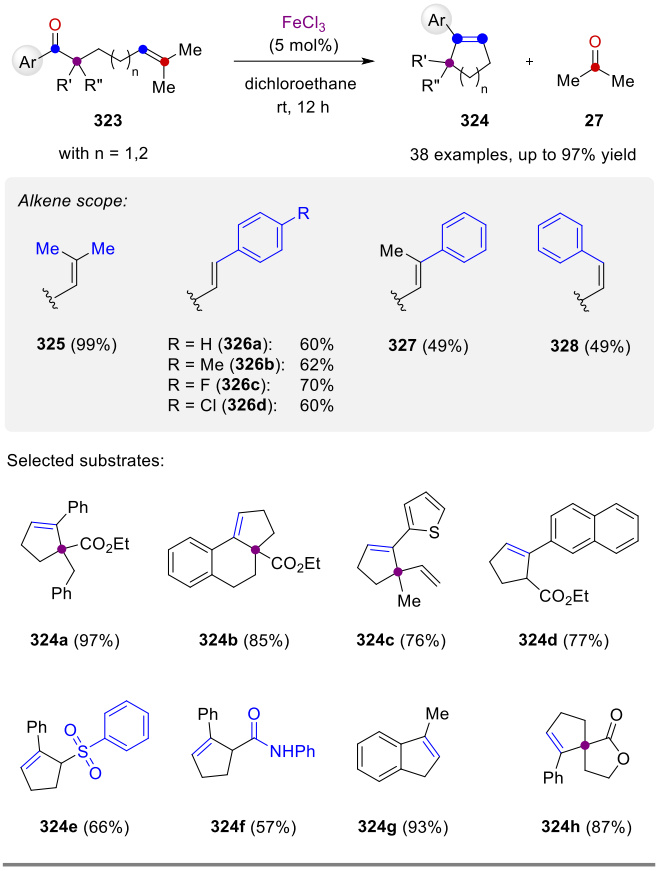
Scheme 54. Initial Studies of Carbonyl-Olefin Ring-Closing Metathesis by Schindler and Coworkers Show Several Lewis Acids Capable of Promoting the Desired Transformation



entry	Lewis acid (1.0 equiv)	yield **320** (%)	yield **321** (%)	yield **322** (%)	conv. (%)
1	$ZnCl_2$	-	-	-	0
2	$SnCl_4$	47	24	-	99
3	$InCl_3$	-	78	-	99
4	$GaCl_3$	-	71	-	99
5	$FeCl_3$	-	50	-	99
6	$AlCl_3$	-	-	66	99

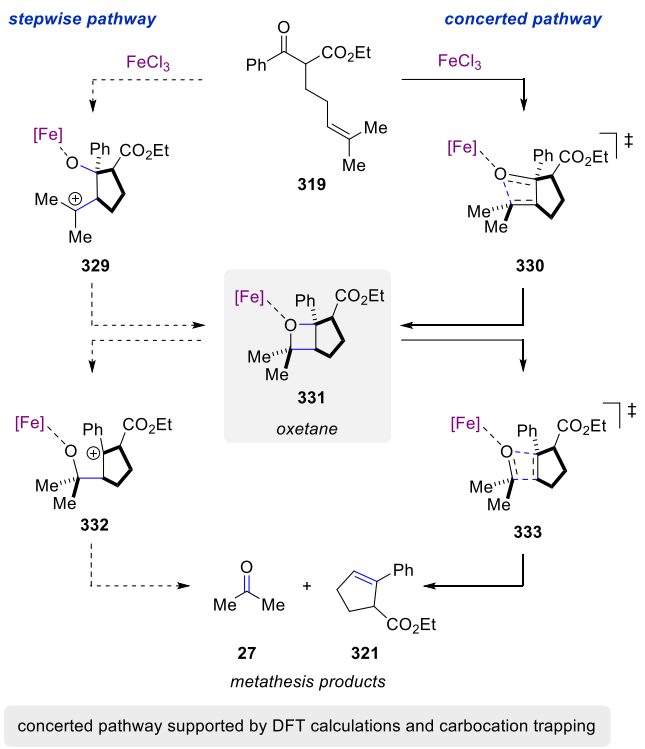
In 2016, Schindler and co-workers reported a carbonyl-olefin ring-closing metathesis reaction relying on $FeCl_3$ as Lewis acid catalyst, which proved uniquely effective for the synthesis of 5-membered rings.[99-102,103,104] Initial studies relied on the investigation of β-ketoester **319** with a variety of distinct Lewis acid in stoichiometric reactions (Scheme 54). While weak Lewis acids, such as $ZnCl_2$, resulted in no reactivity, strong Lewis acids including $AlCl_3$ formed the hydrochlorination product **322** exclusively in 66%. Importantly, several Lewis acids, such as $SnCl_4$, $InCl_3$, $GaCl_3$, and $FeCl_3$ proved capable in promoting the desired carbonyl-olefin metathesis reaction while $FeCl_3$ proved superior and resulted in quantitative formation of cyclopentene **321**.

Scheme 55. Scope of the $FeCl_3$-Catalyzed Carbonyl-Olefin Ring-Closing Metathesis Reaction



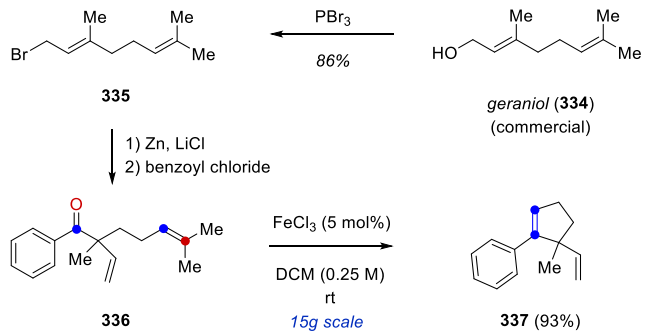
Reaction conditions relying on catalytic quantities of $FeCl_3$ (5 mol%) in dichloroethane at room temperature were ultimately identified as optimal (Scheme 55). While prenylated alkenes (**325**) proved superior and formed the desired carbonyl-olefin ring-closing metathesis products quantitatively, styrene derivatives (**326a, 327**) and their electron-rich (**326b**) and electron-poor analogs (**326c-d**) formed the metathesis products in 49 to 70% yield. Importantly, (*Z*)-styrene (**328**) was identified as a viable substrate in $FeCl_3$-catalyzed carbonyl-olefin ring-closing metathesis reactions albeit resulting in lower yields than the corresponding (*E*)-analog **326a**. The initial report by the Schindler laboratory included 38 examples of 5-membered rings systems formed in up to 97% yield, while a limited number of successful 6-membered ring formations were shown to proceed in up to 71% yield. Notably, several functional groups, including esters, amides, ethers, lactones, halogens, and sulfones were tolerated well under the optimal reaction conditions resulting in a variety of structurally distinct cyclic products.

Scheme 56. Two Mechanistic Alternatives for $FeCl_3$-Catalyzed Carbonyl-Olefin Ring-Closing Metathesis



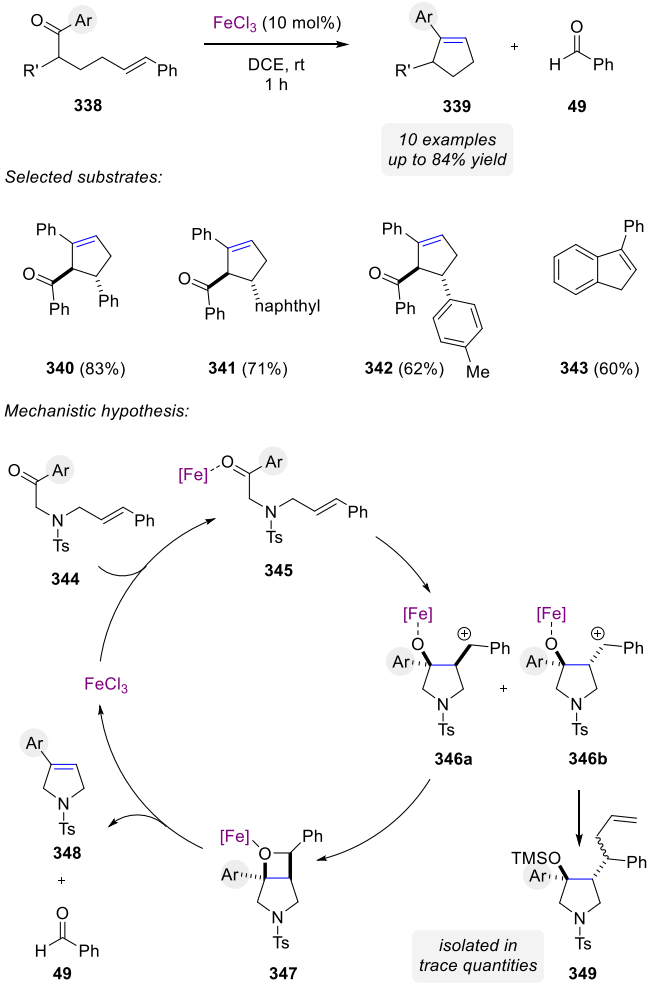
This initial report suggested two possible mechanistic scenarios for catalytic carbonyl-olefin ring-closing metathesis reactions resulting in the formation of cyclopentenes. Similar to earlier reports relying on stoichiometric quantities of Lewis acids by Bickelhaupt[95] and Schmalz,[98] a reaction pathway based on intermediate carbocations was considered (Scheme 56). Specifically, upon coordination of the Lewis acid catalyst to β-ketoester **319**, initial carbon-carbon bond formation would lead to carbocation **329**, which upon intramolecular addition results in the formation of oxetane **331**. Subsequent Lewis acid-mediated fragmentation of the carbon-oxygen bond in **331** results in the benzylic carbocation **332** that undergoes carbon-carbon bond rupture to form the carbonyl-olefin metathesis product **321** and acetone **27** as byproduct. However, carbocation trapping experiments conducted by the Schindler group relying on the addition of intramolecular and intermolecular nucleophiles did not give rise to any compounds indicative of the presence of intermediate carbocations and instead gave rise to the desired carbonyl-olefin metathesis products as the exclusive compounds formed. Based on these results, a second mechanistic hypothesis was suggested that similarly relied on the initial Lewis acid-catalyzed activation of β-ketoester **316** albeit in an asynchronous, concerted [2+2]-cycloaddition that does not rely on carbocation intermediates to form oxetane **331**. An ensuing asynchronous, concerted retro [2+2]-cycloaddition gives rise to the desired carbonyl-olefin metathesis products **321** and **27**. Computational investigations based on DFT studies supported the asynchronous, concerted pathway for oxetane formation and fragmentation *via* [2+2]-cycloadditions that does not rely on carbocation intermediates.

Scheme 57. Organic Synthesis Procedure Developed for $FeCl_3$-Catalyzed Carbonyl-Olefin Ring-Closing Metathesis



Notably, a scalable approach for this $FeCl_3$-catalyzed carbonyl-olefin metathesis was reported by the Schindler group in 2018 as an Organic Synthesis procedure that resulted in 93% yield of the desired metathesis product **337** on a 15 g scale (Scheme 57).[105] The revised reaction conditions were modified to be conducted at higher concentration and purification of the product was conducted by distillation to avoid column chromatography.

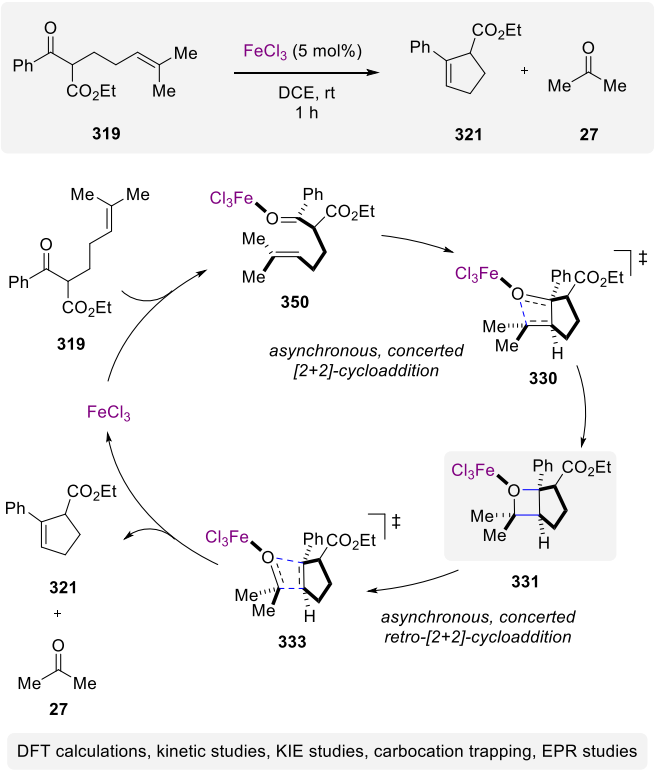
Scheme 58. $FeCl_3$-Catalyzed Carbonyl-Olefin Ring-Closing Metathesis by Li and Coworkers



In 2016, Li and coworkers published an $FeCl_3$-catalyzed carbonyl-olefin ring-closing metathesis reaction that proved efficient for the synthesis of 5-membered rings and a selection of 6-membered ring products in up to 84% yield.[106] The initial report relied on

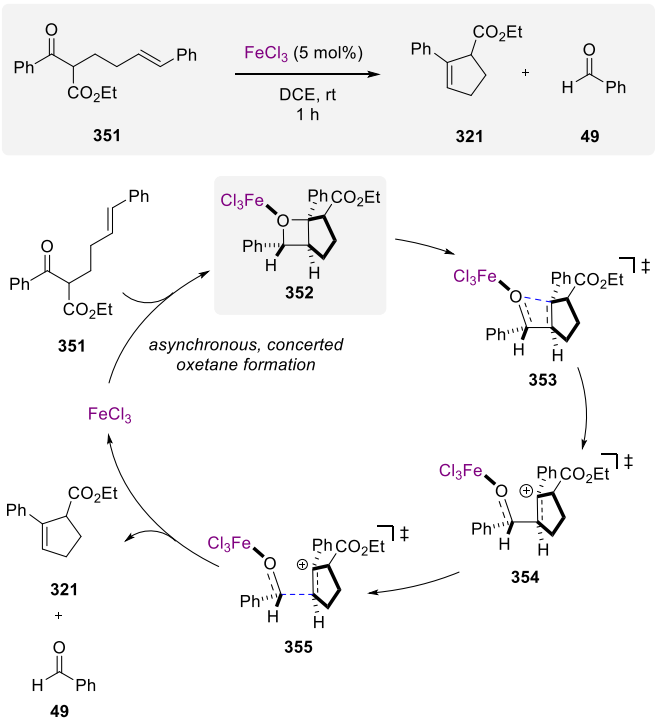
two sets of reaction conditions, specifically carbocyclic structures were formed with 10 mol% $FeCl_3$ as the Lewis acid catalyst in dichloroethane at ambient temperatures, while nitrogen-containing 5-membered rings proceeded with catalyst loadings of 20 mol% and the addition of 5.0 equivalents of allyltrimethylsilane (Scheme 58). Interestingly, the approach reported by Li and coworkers relies on styrene derivatives as alkene components for carbonyl-olefin metathesis with the proposed role of allyltrimethylsilane in the reaction mixture being trapping of the benzaldehyde byproduct. Li and coworkers postulate a stepwise reaction mechanism that relies on the initial activation of the substrate **344** with the Lewis acid catalyst to form Lewis acid-base complex **345**. Subsequent carbon-carbon bond formation gives rise to diastereomeric carbocations **346a** and **346b**, of which **346a** results in the formation of oxetane **340** and subsequent fragmentation to give rise to the metathesis products **348** and **49**. Silylether **349** was isolated in trace quantities from the reaction mixture, which is postulated to arise upon trapping of carbocation **346b** with allyltrimethylsilane.

Scheme 59. Mechanistic Investigations of Prenylated β-Ketoesters in $Fecl_3$-Catalyzed Carbonyl-Olefin Metathesis by Schindler, Devery, Zimmerman, and Coworkers



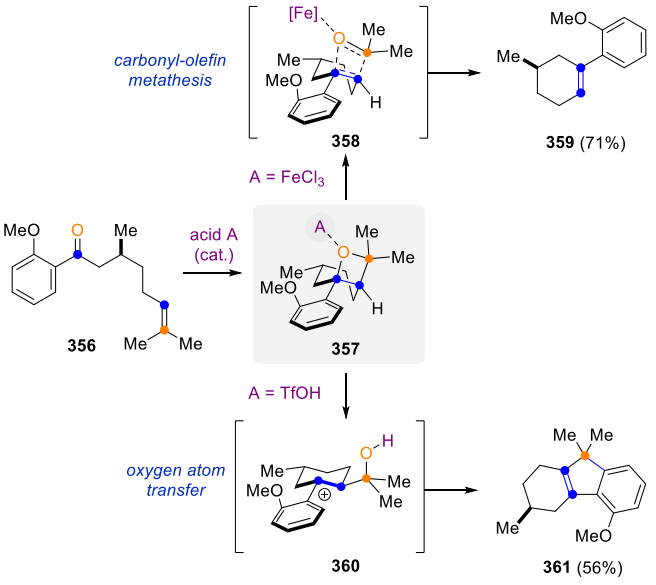
In 2017, Schindler, Devery, Zimmerman, and coworkers conducted detailed mechanistic studies of prenylated alkenes and styrene-derived alkenes as substrates for $FeCl_3$-catalyzed carbonyl-olefin ring-closing metathesis that has led to two distinct proposed catalytic cycles depending on the olefin substitution.[107] Results obtained in EPR, kinetic, computational and experimental synthetic studies suggest that the $FeCl_3$ catalyst binds at the carbonyl moiety of the substrate without an electron transfer event for both types of substrates. Additionally, metathesis occurs for a variety of $FeCl_3$ sources regardless of hydration of the metal center while HCl, as a possible hydrolysis product of $FeCl_3$, does not catalyze the transformation. Specifically, prenylated substrates **319** undergo carbonyl-olefin metathesis upon binding of the $FeCl_3$ catalyst to the carbonyl oxygen to form Lewis acid-base complex **350** as the catalyst resting state (Scheme 59). Asynchronous, concerted [2+2]-cycloaddition of **350** *via* **330** results in the formation of intermediate oxetane **331**, which undergoes asynchronous, concerted retro [2+2]-cycloaddition in the product-forming step.

Scheme 60. Mechanistic Investigations of Styrenyl-derived β-Ketoesters in $FeCl_3$-Catalyzed Carbonyl-Olefin Metathesis by Schindler, Devery, Zimmerman, and Coworkers



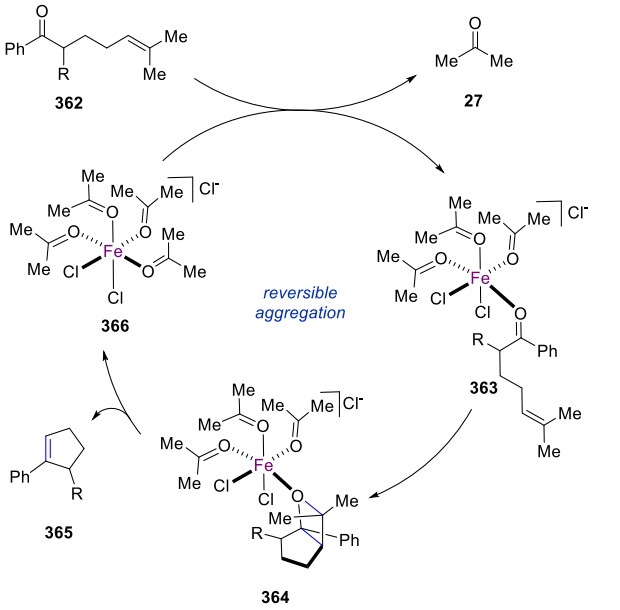
In comparison to their prenylated analogs, substrates bearing a styrenyl fragment **351** undergo oxetane fragmentation *via* a distinct reaction path (Scheme 60). While β-ketoesters **351** undergo activation of the carbonyl oxygen upon binding to the $FeCl_3$ catalyst to form the corresponding Lewis acid-base complex and subsequent asynchronous, concerted [2+2]-cycloaddition to result in oxetane **352**, its fragmentation pathway differs. Specifically, heterolysis of oxetane **352** results carbocation **353** as a charged intermediate that subsequently eliminates metathesis product **321** and benzaldehyde **49** as the byproduct.

Scheme 61. Carbonyl-Olefin Metathesis (**359**) *versus* Interrupted Carbonyl-Olefin Metathesis Reactions (**361**).



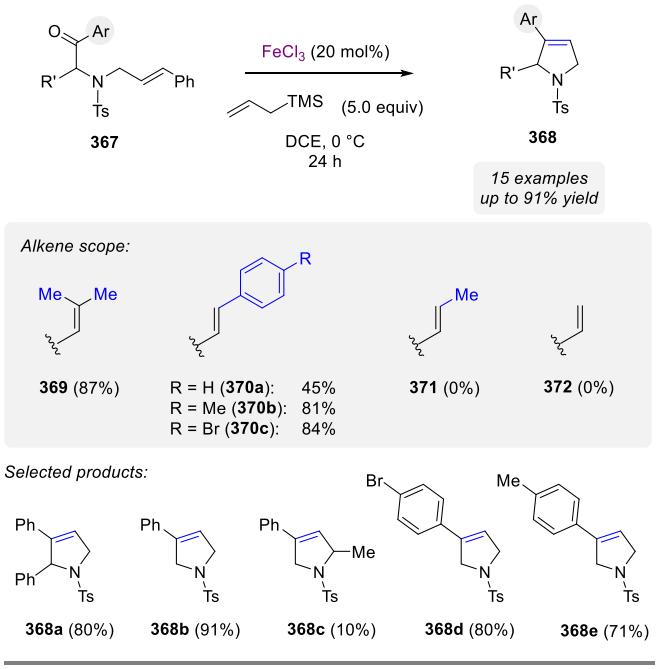
In 2018, the Schindler research group reported an alternative oxetane fragmentation path for prenylated alkenes **356** that interrupts previously established carbonyl-olefin metathesis reactions paths (Scheme 61).[108] While aryl ketone **356** undergoes catalytic carbonyl-olefin metathesis relying on $FeCl_3$ as Lewis acid catalyst to give rise to the metathesis product **359** in 71 % yield, conversion of **356** with catalytic amounts of triflic acid results in the exclusive formation of tetrahydrofluorene **361** in 56% yield. Mechanistic studies suggest that both reaction paths proceed *via* intermediate oxetane **357** although in the Brønsted acid-catalyzed reaction path oxetane fragmentation occurs stepwise to form carbocation **360** that ultimately gives rise to **361** *via* intramolecular Friedel-Crafts alkylation. These results provide additional support for an asynchronous, concerted oxetane fragmentation of prenylated substrates in carbonyl-olefin metathesis reactions that does not proceed through a carbocation intermediate.

Scheme 62. $FeCl_3$ Catalyst Behavior and Solution Structure Investigated by Devery and Coworkers



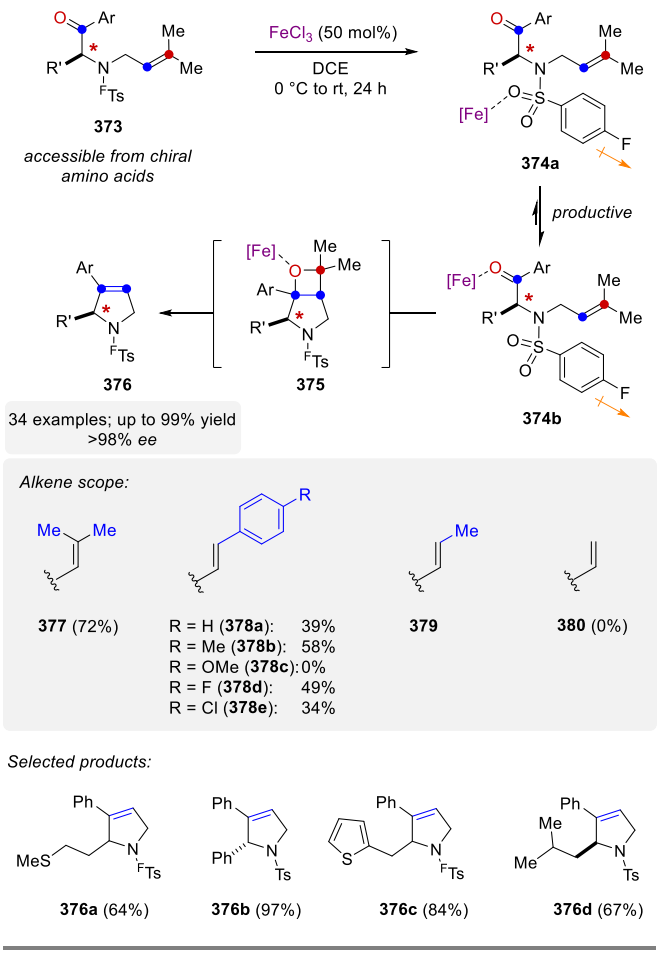
In 2019, the Devery group investigated the solution structure and catalyst behavior of Lewis acids including $FeCl_3$ and $GaCl_3$ for ring-closing carbonyl-olefin metathesis in kinetic, spectroscopic, colligative, and crystallographic studies.[109] While $GaCl_3$ exhibits a classic 1:1 Lewis-acid-Lewis base coordination event, $FeCl_3$ is capable of forming aggregate **363** upon coordination of acetone **27** in solution, which was found to be catalytically active and capable of binding substrate **362** (Scheme 62).

Scheme 63. Formation of 2,5-Dihydropyrroles in $FeCl_3$-Catalyzed Carbonyl-Olefin Metathesis by Li and Coworkers



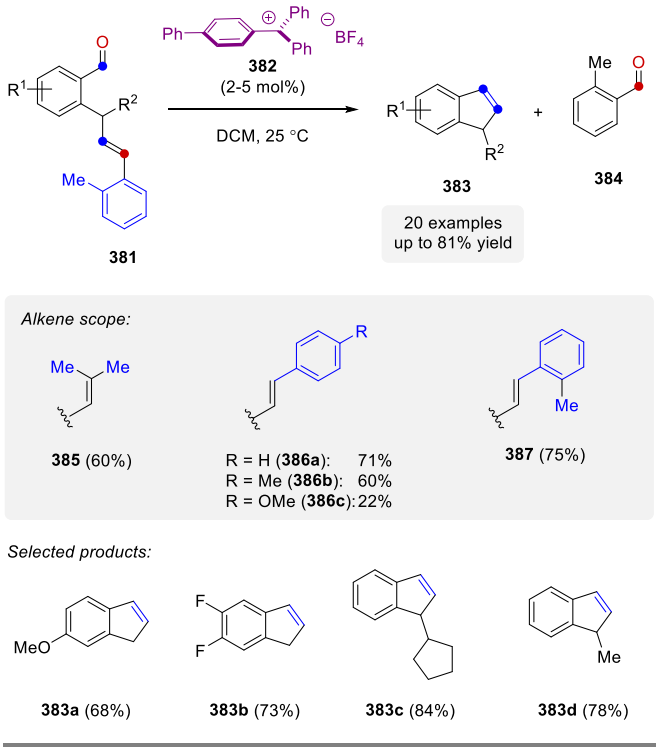
The original report on $FeCl_3$-catalyzed carbonyl-olefin metathesis by Li an coworkers in 2016 also described the formation of 2,5-dihydropyrroles starting from the corresponding styrenyl precursors **367** bearing tosyl-protected secondary amines (Scheme 63).[106] The transformation relies on 20 mol% $FeCl_3$ as the Lewis acid catalyst and the addition of 5.0 equivalents allyltrimethylsilane to sequester the benzaldehyde byproduct formed. Prenylated alkenes (**369**) were identified as viable substrates resulting in 87% yield of the metathesis products together with electron-neutral (**370a**), -rich (**370b**), and –poor (**370c**) styrenes. Notably, the optimal reaction conditions proved efficient for a variety of structurally distinct 2,5-dihydropyrroles resulting in the desired products in up to 91% yield.

Scheme 64. *N*-Containing Substrates for Carbonyl-Olefin Metathesis by Schindler and Coworkers



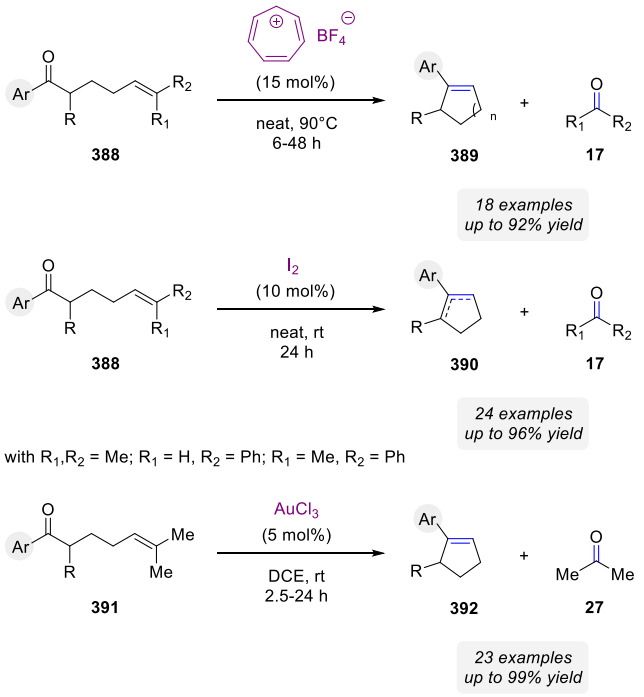
In 2018, the Schindler group reported a related investigation into the ring-closing carbonyl-olefin metathesis of N-containing substrates to access chiral 3-aryl-2,5-dihydropyrroles relying on commercially available amino acids as chiral pool reagents and $FeCl_3$ as Lewis acid catalyst (Scheme 64).[110-111] Initial experimental investigations relying on these substrates had resulted in low yields of the desired products while high loadings of $FeCl_3$ were required. Following their hypothesis that the additional Lewis basic sites present in the amine substrates represent competitive Lewis basic binding sites for the $FeCl_3$ catalyst, experimental and computational investigations were conducted, which ultimately corroborated this hypothesis. The Schindler laboratory postulated that attenuating the electronic properties of the sulfonamide moiety by adding electron-withdrawing substituents to the aromatic ring could disfavor catalyst sequestration and prevent stalling of the metathesis reaction. Evaluation of a variety of electronically distinct sulfonamide-protecting groups based on the hypothesis led to the identification of the 4-trifluoromethylbenzenesulfonyl functionality (^{F}Ts in **373**, Scheme 64). Interestingly, this electron-deficient sulfonamide renders the protected amine as less Lewis basic and consequently a less competitive binder (**374a** vs. **374b**) for the $FeCl_3$ Lewis acid resulting in yields of up to 99%. Additionally, the enantiomeric excess of the substrates was maintained throughout the course of the transformation resulting in the formation of the desired chiral 2,5-dihydropyrroles in >98% *ee*. Similar to earlier reports by Li and coworkers, prenyl-derived alkenes **377** proved superior as alkene moieties while styrene derivatives (**378a-e**) resulted in diminished overall yields. The generality of this approach was demonstrated in 34 examples of electronically and sterically distinct 2,5-dihydropyrroles formed in up to 99% yield and >98% *ee*. Importantly, the ^{F}Ts-protecting group was readily cleaved under reductive conditions using SmI_2 resulting in the free 2,5-dihydropyrroles while their enantiomeric excess was maintained.

Scheme 65. Carbocation-Catalyzed Carbonyl-Olefin Ring-Closing Metathesis by Franzén and Coworkers



In 2018, the Franzén group was able to develop a carbocation-based carbonyl-olefin ring-closing metathesis reaction to access functionalized indenes relying on 4-phenylphenyl-diphenylmethylium tetrafluoroborate (**382**) as a Lewis acid catalyst (Scheme 65).[112] Interestingly, styrene-derived alkenes (**386a-c**) proved superior as metathesis substrates in this transformation as compared to their prenyl analog (**385**), which ultimately led to the identification of *ortho*-methyl styrenes **387** as optimal substrate class. Specifically, Franzén and coworkers identified weakly donating substituents in the *ortho*-position of the styrene moieties as key structural components to shorten the overall reaction time while reducing competing substrates and product decomposition. The optimized reaction conditions proceeding with 2-5 mol% of 4-phenylphenyl-diphenylmethylium tetrafluoroborate (**382**) as Lewis acid proved general for 20 examples of indenes **383** bearing steric and electronically distinct substitutions resulting in up to 81% yield of the desired carbonyl-olefin metathesis products.

Scheme 66. Approaches to Carbonyl-Olefin Ring-Closing Metathesis Relying on Tropylium Cations, Iodine, and $AuCl_3$ as Lewis Acid Catalysts by Nguyen and Lin

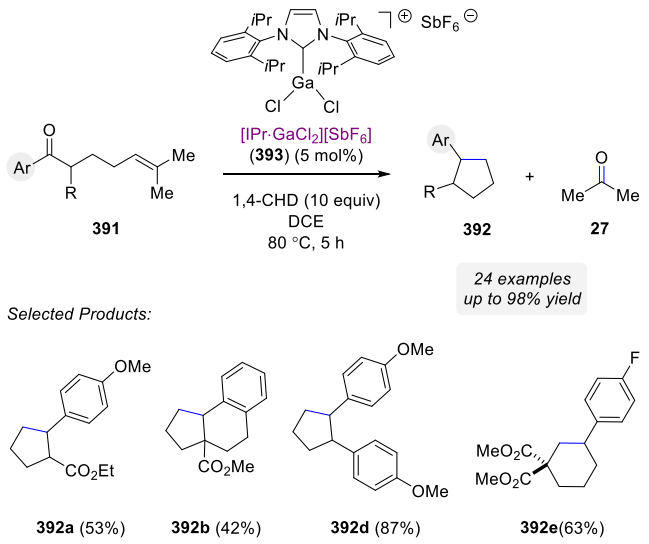


In 2018, Nguyen and coworkers showed that tropylium ions are potent Lewis acid catalysts for carbonyl-olefin ring-closing metathesis resulting in the formation of cyclopentene products (Scheme 66).[113] Reaction optimization studies conducted by the authors identified substrates incorporating prenyl moieties as alkene components as superior compared to their styrenyl analogs, which resulted in a decrease in yield of the desired carbonyl-olefin metathesis product formed. Optimal conditions rely on 15 mol% of the tropylium catalyst at 90 °C for 6-48 hours neat while the generality of this approach was demonstrated in 18 examples resulting in up to 92% yield (**389**, Scheme 66).

In 2019, Nguyen and coworkers built on their prior studies and reported that molecular iodine was similarly capable of catalyzing carbonyl-olefin ring-closing metathesis reactions (Scheme 66).[114] Similarly to their earlier report, the optimal reaction conditions proceed neat albeit at ambient temperatures relying on 10 mol% molecular iodine and result in the formation of 24 examples of functionalized cyclopentene products in up to 96% yield. Based on computational investigations conducted of the I_2-catalyzed carbonyl-olefin ring-closing metathesis reaction, the authors suggest a reaction pathway that proceeds stepwise *via* initial carbon-carbon bond formation between the carbonyl and alkene moiety to result in an intermediate carbocation, which subsequently results in an oxetane that then undergoes ensuing stepwise fragmentation *via* a benzylic carbocation to result in the desired metathesis products.

In 2019, Lin and coworkers reported that catalytic amounts of $AuCl_3$ proved equally efficient as a Lewis acid catalyst for carbonyl-olefin ring-closing metathesis (Scheme 66).[115] The optimal reaction conditions reported are based on 5 mol% $AuCl_3$ and proceed in dichloroethane at ambient temperatures for up to 24 hours. Moreover, these conditions prove general for a variety of functionalized cyclopentenes resulting in up to 99% yield of the carbonyl-olefin ring-closing metathesis products. DFT studies performed by the authors support an asynchronous, concerted [2+2]-cycloaddition and retro [2+2]-cycloaddition *via* intermediate oxetanes while carbocation trapping experiments with MeOH as an exogenous nucleophile did not result in the formation of a new product.

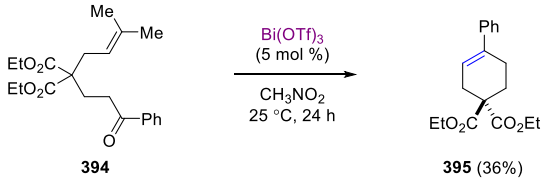
Scheme 67. Carbonyl-Olefin Ring-Closing Metathesis and Transfer Hydrogenation by Gandon and Bour



In 2019, Gandon and Bour reported the combination of catalytic carbonyl-olefin ring-closing metathesis and subsequent transfer hydrogenation relying on the Ga-based metal complex **393** and 1,4-cyclohexadiene (1,4-CHD) as a hydrogen donor (Scheme 67).[116] Notably, the Ga-complex **393** catalyzes the initial carbonyl-olefin ring-closing metathesis reaction and the ensuing hydrogenation resulting in the formation of functionalized cyclopentane products. The generality of this approach is demonstrated in 24 examples resulting in up to 98% yield. Interestingly, products bearing 1,2-disubstitution are formed in diastereomeric ratios ranging from 4:1 to >20:1 d.r. favoring the *cis* products. Based on DFT calculations, the authors suggest a reaction pathway that is promoted by a homodimeric Ga-complex formed, which coordinates to the 1,4-cyclohexadiene to activate it for the subsequent reduction of the metathesis products formed.

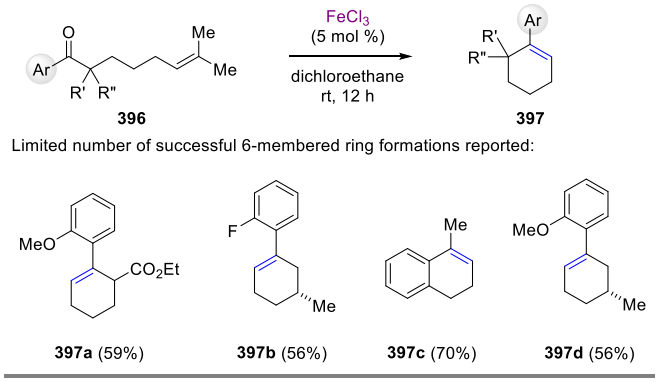
6.2.2 Formation of 6-Membered Rings

Scheme 68. Duñach Observes the Formation of Carbonyl-Olefin Ring-Closing Metathesis Product **395** in Studies of Intramolecular Carbonyl-Ene Reactions



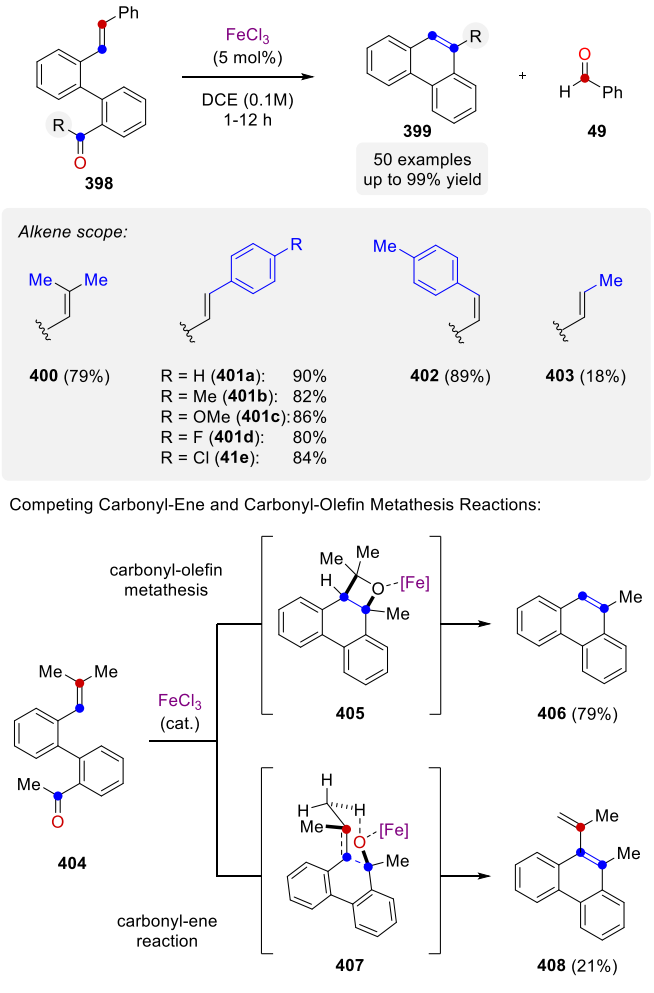
In comparison to carbonyl-olefin ring-closing metathesis reactions resulting in 5-membered rings, the analogous transformations forming their higher order homologs in the form of 6- or 7-membered ring products are much less developed. Successful, general reports for Lewis acid-catalyzed carbonyl-olefin ring-closing metathesis reactions currently center on polyaromatic hydrocarbons[117] and tetrahydropyridines as products,[118] while efficient strategies giving rise to functionalized cyclohexene products have only recently been reported. However, isolated early reports for Lewis acid-catalyzed carbonyl-olefin metathesis reactions for the synthesis of cyclohexenes do exist. For example, studies by Duñach and coworkers in intramolecular carbonyl-ene reactions described the formation of cyclohexene **395** from aryl ketone **394** formed as a byproduct in 36% yield upon conversion with 5 mol% $Bi(OTf)_3$ (Scheme 68).[119]

Scheme 69. Limited Examples for Cyclohexene Products Formed in Catalytic Carbonyl-Olefin Ring-Closing Metathesis by Schindler and Coworkers



Furthermore, Schindler and coworkers' early report on $FeCl_3$-catalyzed carbonyl-olefin ring-closing metathesis reactions[99] included a limited scope of functionalized cyclohexene products formed (**397a-d**, Scheme 69). Although these products were formed in up to 70% yield, they remained isolated examples with substrates lacking *ortho*-substitution on the aryl moiety resulting in significantly diminished yields.

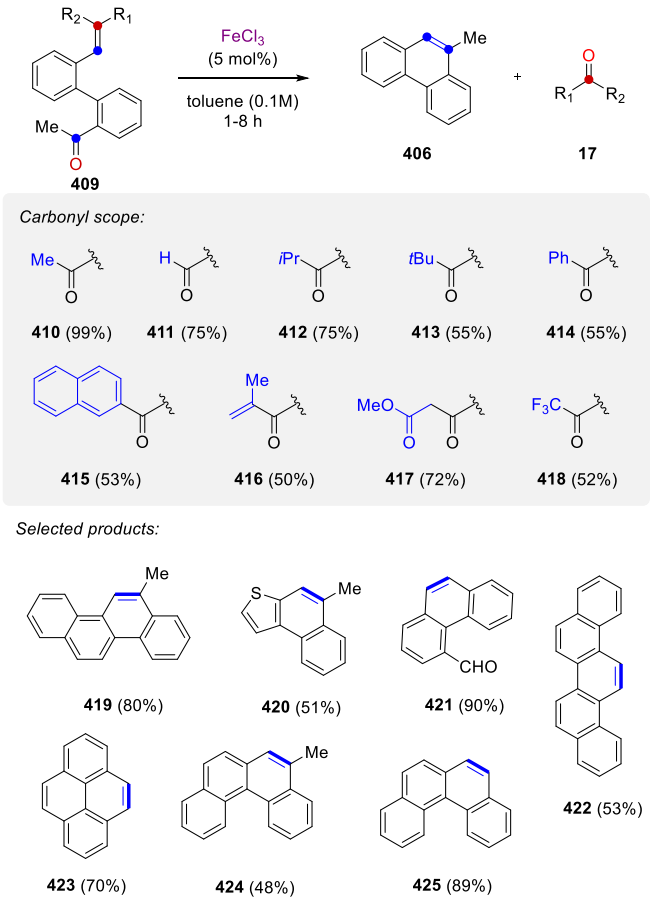
Scheme 70. Carbonyl-Olefin Metathesis Towards Polycyclic Aromatic Hydrocarbons by Schindler and Coworkers



Following the development of the ring-closing carbonyl-olefin metathesis reaction of aryl ketones, the Schindler group reported its application for the synthesis of polycyclic aromatic compounds (PACs) in 2017.[117] PACs are important structural motifs in natural

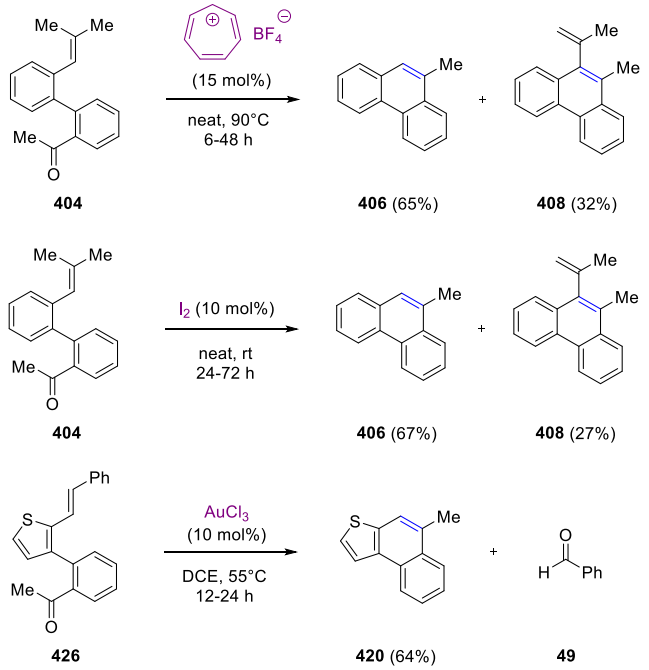
product synthesis, materials science, and asymmetric catalysis. The reaction conditions originally developed for carbonyl-olefin ring-closing metathesis of cyclopentenes relying on 5 mol% $FeCl_3$ in dichloroethane at ambient temperatures proved efficient in giving rise to a wide variety of electronically and structurally distinct polyaromatic hydrocarbons (Scheme 70). The synthetic generality of this approach was demonstrated in 50 examples proceeding in up to 99% yield. Interestingly, prenylated alkenes (**400**) resulted in overall lower yields of the metathesis products compared to the corresponding styrenes (**401a-e**). Subsequent investigations showed that although carbonyl-olefin metathesis is the predominant reaction pathway, prenylated alkenes can undergo competing carbonyl-ene reactions (**407**) resulting in 21% yield of alkene **408** starting from ketone **404**. Subsequent efforts by Schindler and coworkers focused on substrates bearing styrenyl alkenes as these cannot undergo competing carbonyl-ene reactions. Notably, during the course of these optimizations, an oxetane product obtained from a trifluoromethyl ketone substrate was isolated in 45% yield and characterized by X-ray diffraction analysis providing further support for oxetanes as reactive intermediates in catalytic carbonyl-olefin metathesis reactions.

Scheme 71. Investigation of the Carbonyl Scope in Catalytic Carbonyl-Olefin Metathesis Reactions by Schindler and Coworkers



Additionally, detailed studies focused on the evaluation of the carbonyl moiety were conducted and identified ketones (**410**), aldehydes (**411**), as well as ketones bearing sterically constraint substituents as viable substrates (**412-413**, Scheme 71). Moreover, ketones bearing two aromatic substituents (**414** and **415**) provided moderate yields of the metathesis products, while enones (**416**) as well 1,3-diketones (**417**), and electron deficient ketones (**418**) resulted in 50%, 72%, and 52% yield, respectively.

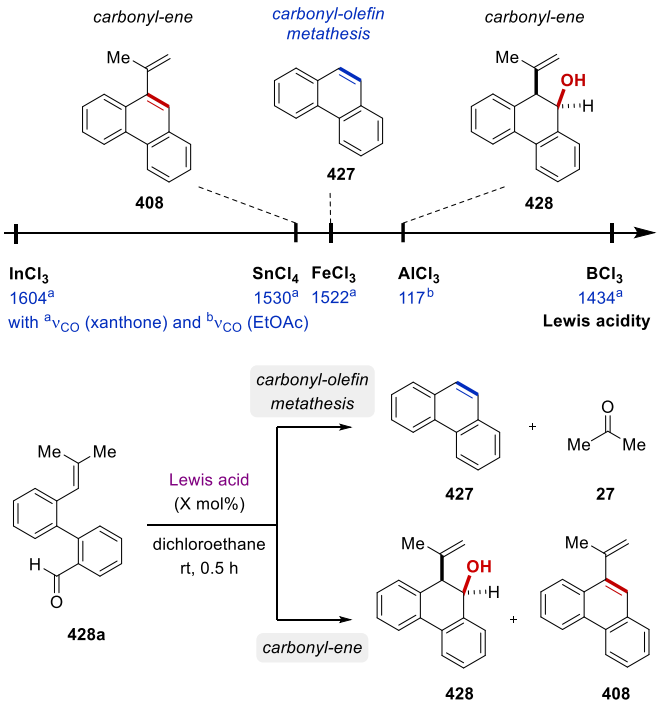
Scheme 72. Approaches to Carbonyl-Olefin Ring-Closing Metathesis Relying on Tropylium Cations, Iodine, and $AuCl_3$ as Lewis Acid Catalysts for the Formation of Polyaromatic Hydrocarbons by Nguyen and Lin



In their 2018 report on carbonyl-olefin ring-closing metathesis reactions relying on tropylium ions as Lewis acid catalysts, the Nguyen group also demonstrated the compatibility of their reaction conditions with the synthesis of polyaromatic systems (Scheme 72).[113] Under the reported reaction conditions, prenylated ketone **404** results in the formation of metathesis product **406** in 65% yield together with carbonyl-ene product **408** in 32% yield. Similarly, the 2019 report by Nguyen and coworkers relying on iodine as Lewis acid catalyst included an example resulting in polyaromatic metathesis product **406** in 67% yield from aryl ketone **404** while the carbonyl-ene byproduct **408** was formed in 27% yield (Scheme 72).[114]

The report on $AuCl_3$-catalyzed carbonyl-olefin ring-closing metathesis by Lin and coworkers also included an example resulting in a polyaromatic system demonstrating the compatibility of their optimal conditions with this substrate class (Scheme 72).[1145] Specifically, ketone **426** resulted in 64% yield of thiophene when converted with 10 mol% $AuCl_3$ in dichloroethane at 55 °C.

Scheme 73. Divergent Reactivity Observed in Carbonyl-Olefin Metathesis and Carbonyl-Ene Reactions is not Exclusively Explained by Lewis Acidity as Reported by Schindler and Reid

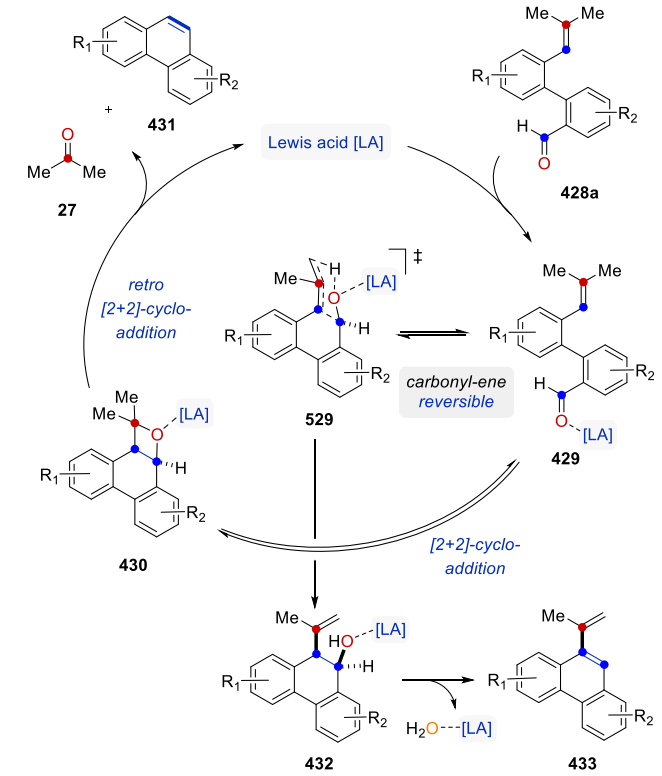


entry	Lewis acid (mol%)	yield **427** (%)	yield **428** (%)	yield **408** (%)	conv. (%)
1	$FeCl_3$ (10)	33	-	19	99
2	Me_2AlCl (5)	-	94	5	99
3	$SnCl_4$ (20)	3	-	95	99

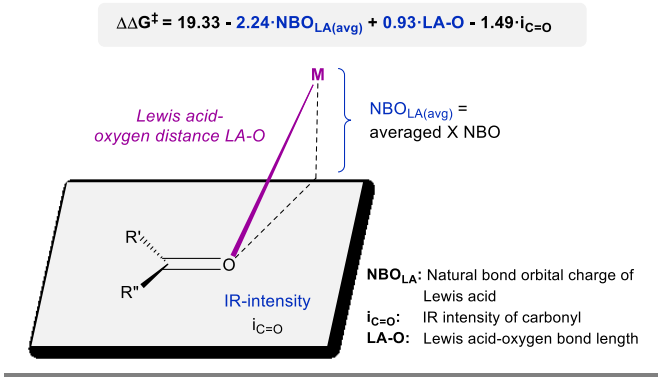
In 2020, Schindler, Reid and coworkers followed up on their initial report on catalytic carbonyl-olefin metathesis for the synthesis of polyaromatic hydrocarbons and focused on the evaluation of additional Lewis acid catalysts for this transformation.[120] Importantly, preliminary studies had revealed that the conversion of aldehyde **428a** bearing a prenylated alkene moiety with either weaker or stronger Lewis acids compared to $FeCl_3$ favored the carbonyl-ene reaction pathway, while $FeCl_3$ proved unique in promoting predominantly carbonyl-olefin metathesis (Scheme 73). Specifically, catalytic amounts of $SnCl_4$ formed the dehydrated carbonyl-ene product **408** in 95% yield and stoichiometric amounts of Me_2AlCl resulted in 94% yield of unsaturated alcohol **428** as the carbonyl-ene product, while 10 mol% $FeCl_3$ provided 33% yield of carbonyl-olefin metathesis product **427** and 19% yield of the dehydrated carbonyl-ene product **408**. The fact that even simple Lewis acids demonstrated remarkable selectivity in differentiating between both reaction paths led the authors to investigate the origins of this bias to understand the specific catalyst requirements to favor one reaction path over the other. In the course of their studies, Schindler, Reid and coworkers developed predictive multivariate linear regression models based on kinetic and thermodynamic information obtained in DFT calculations of the complex potential energy surfaces of carbonyl-olefin metathesis and carbonyl-ene reactions as competing reaction paths.

Scheme 74. Mechanistic Hypothesis for Competing Carbonyl-Olefin Metathesis and Carbonyl-Ene Reactions of Biaryl Aldehydes by Schindler and Reid

Mechanistic Hypothesis:



A general predictive model for carbonyl-olefin metathesis:

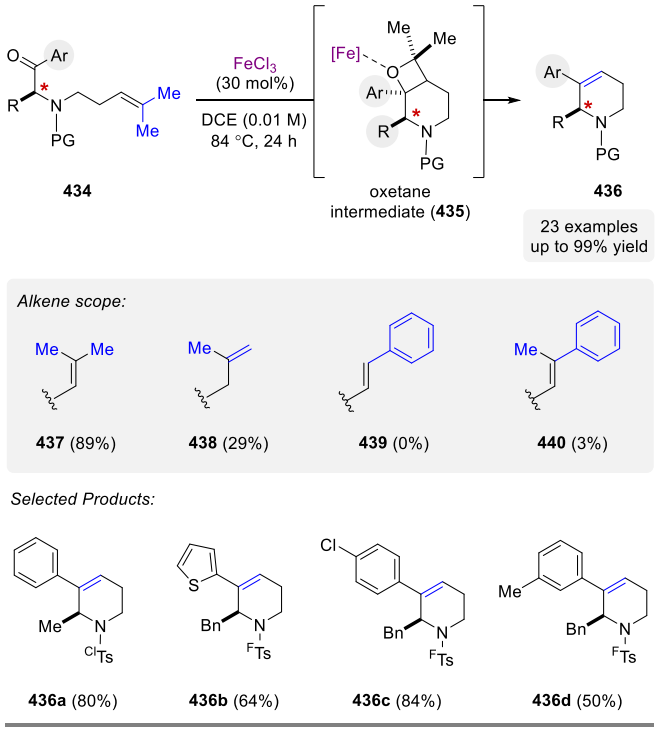


Importantly, upon binding of the biaryl aldehyde **428a** to the Lewis acid, the Lewis acid-base complex **429** is formed, which can undergo a reversible carbonyl-ene reaction with both $FeCl_3$ and Me_2AlCl as Lewis acids to form unsaturated alcohol **432** (Scheme 74). Importantly, alcohol **432** is isolated as the exclusive product with Me_2AlCl as Lewis acid since the competing [2+2]-cycloaddition from **429** is prohibitively high in energy and thus results in the carbonyl-ene reaction as the predominant reaction pathway. In comparison, unsaturated alcohol **432** is formed reversibly when relying on $FeCl_3$ as Lewis acid catalyst in addition to the barrier of competing [2+2]-cycloaddition from **429** being significantly lower compared to the Me_2AlCl promoted reaction pathway. Consequently, conversion of biaryl aldehyde **428a** with catalytic amounts of $FeCl_3$ results in the formation of carbonyl-olefin metathesis product **431** as the thermodynamic product.

Subsequent efforts centered on the development of multivariate linear regression models to describe the competing reaction pathways. Notably, carbonyl-olefin metathesis and carbonyl-ene reactivity could be correctly predicted based on a set of key parameters for both the substrate and Lewis acid employed, which showed that metathesis reactivity displayed a higher dependency

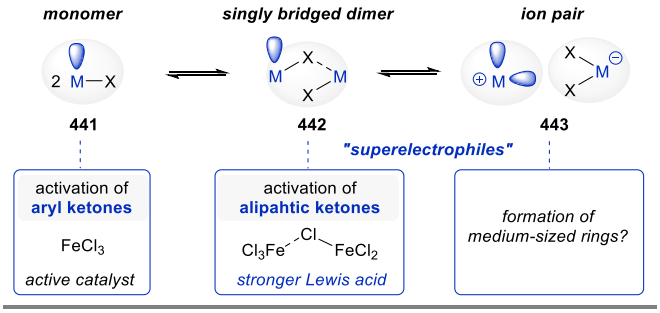
on the choice of Lewis acid employed, whereas carbonyl-ene reactivity was determined to be more substrate dependent. Since carbonyl-olefin metathesis was found to be predominantly determined by the Lewis acid structure, models describing this reactivity mode were expected to be able to adequately predict the reaction barriers for a diverse set of metathesis substrates. Based on descriptors for Lewis acid and substrate from the preceding parameter set, a secondary model for carbonyl-olefin metathesis reaction was developed that relied on three terms centered on the Lewis acid and carbonyl subunit of the substrate (Scheme 74). Specifically, the energy barriers for aryl ketones undergoing Lewis acid-catalyzed carbonyl-olefin metathesis can be predicted based on the IR intensity of the carbonyl ($i_{C=O}$), the Lewis acid-oxygen bond length (LA-O), and the natural bond orbital charge of the Lewis acid ($NBO_{LA(avg)}$). Interestingly, the Lewis acid-oxygen distance was identified as an important contributor in the reactivity of distinct Lewis acids during X-ray crystallographic studies of Lewis acid-carbonyl complexes conducted in 1990 by Schreiber and coworkers.[121]

Scheme 75. Tetrahydropyridines *via* $FeCl_3$-Catalyzed Carbonyl-Olefin Metathesis by Schindler and Coworkers



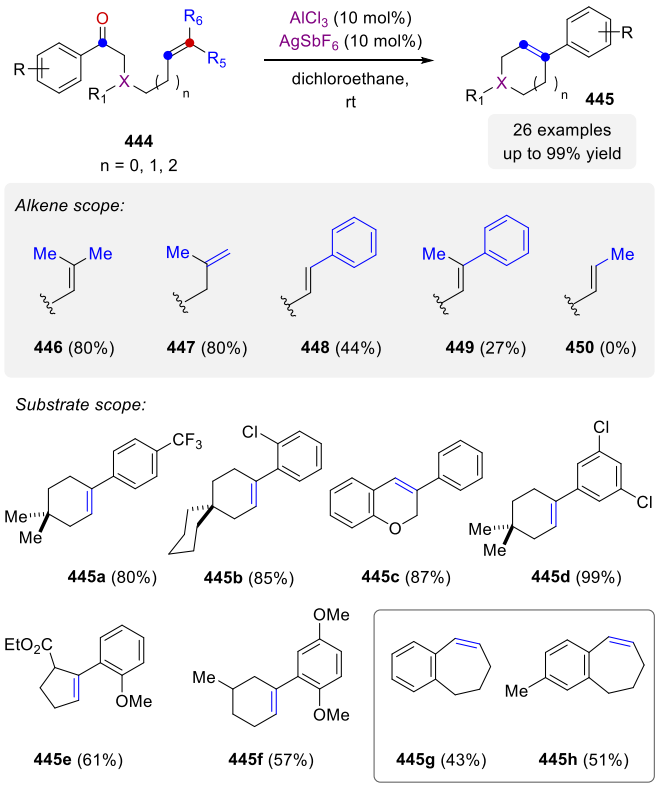
The Schindler group reported in 2020 the $FeCl_3$-catalyzed formation of functionalized tetrahydropyridines **436**.[118] Amino acids serve as chiral pool reagents to access *N*-containing aryl ketones **434** using a variety of electron-poor sulfonamide protecting groups (Scheme 75). Electron-deficient tosylamides functioning as protecting groups for the secondary amines were identified as superior and utilized to promote the desired transformation for a range of 23 substrates proceeding in up to 99% yield. The functionalized metathesis products could be further diversified through a reductive deprotection strategy relying on SmI_2 to remove the sulfonamide protecting groups in high yield while maintaining the enantiomeric excess of the products. Notably, prenyl-derived alkenes (**437**) and terminal alkenes (**438**) capable of isomerizing *in situ* were shown to be the only viable alkene substrates for the synthesis of tetrahydropyridines *via* catalytic carbonyl-olefin metathesis while their stryenyl analogs (**439** and **440**) resulted in no formation of the desired products.

Scheme 76. Lewis Acidic "Superelectrophiles" as Stronger Catalysts for Carbonyl-Olefin Metathesis as Suggested by Schindler and Coworkers



In 2020, Schindler and coworkers were able to extend the scope of 6-membered ring products formed in Lewis acid-catalyzed carbonyl-olefin metathesis reactions from polyaromatic hydrocarbons and tetrahydropyridines to functionalized cyclohexenes accessible from acyclic arylketone substrates.[122] Their reaction design is based on Lewis acidic "superelectrophiles"[123-125] and observations made during the development of carbonyl-olefin metathesis reactions of less reactive aliphatic ketones.[126] Accompanying mechanistic investigations had revealed a second order dependence in $FeCl_3$ and ultimately identified singly bridged dimers (**442**) formed upon *in situ* association of $FeCl_3$ monomers (**441**) as active catalytic species, which together are stronger than the individual $FeCl_3$ monomers (Scheme 76). Schindler and coworkers hypothesized that ion pairs **443** resulting upon heterolytic cleavage of the C-X bond in dimers **442** could function as even stronger Lewis acid catalysts and activate the less reactive acyclic arylketone substrates for carbonyl-olefin metathesis reactions to form cyclohexene products.

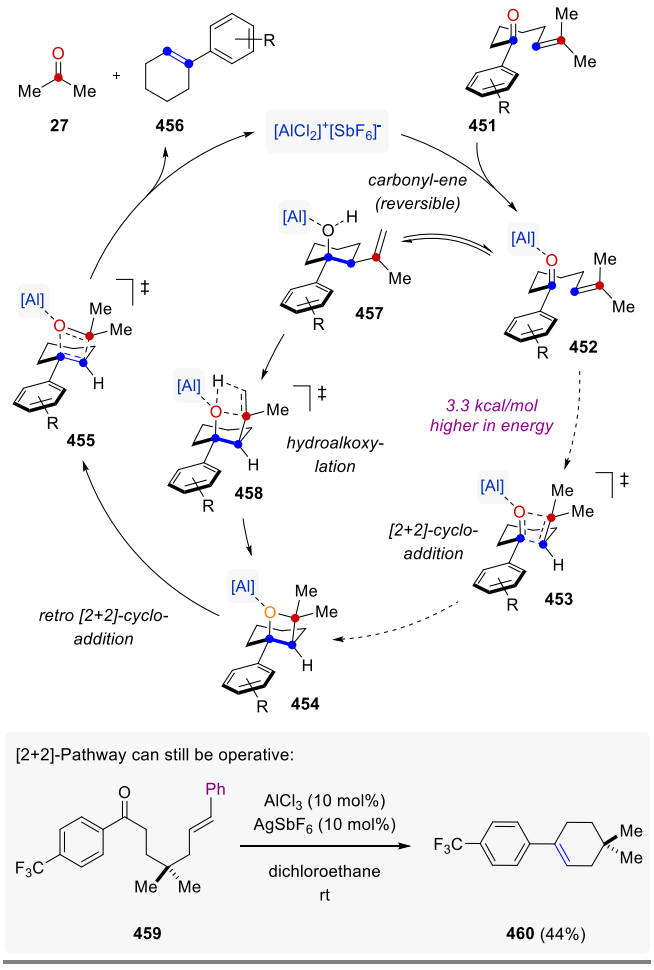
Scheme 77. Formation of 6-Membered Rings from Acyclic Arylketones developed by Schindler and coworkers



Extensive reaction optimization ultimately revealed that heterobimetallic ion pairs resulting upon chloride abstraction from $AlCl_3$ with Ag(I) additives, such as $AgSbF_6$, are capable of promoting the desired transformation in up to 99% yield as shown for 26 examples while standard Lewis acids including $FeCl_3$ resulted in low yields of less than 20% (Scheme 77). Importantly, the addition of $AgSbF_6$ to $AlCl_3$ leads to the *in situ* formation of the ion pair $[AlCl_2][SbF_6]$, which functions as Lewis acidic superelectrophiles.

Prenylated alkenes (**446**) and terminal alkenes (**447**) capable of isomerizing *in situ* while resulting in acetone as the metathesis byproduct proved superior forming the desired metathesis products in 80% yield. In comparison, styrene derivatives **448** and **449** resulted in diminished yields of 44% and 27%, respectively. Notably, the reaction conditions also proved viable for a limited number of 7-membered ring products **445g** and **445h** formed in 43% and 51% yield, respectively.

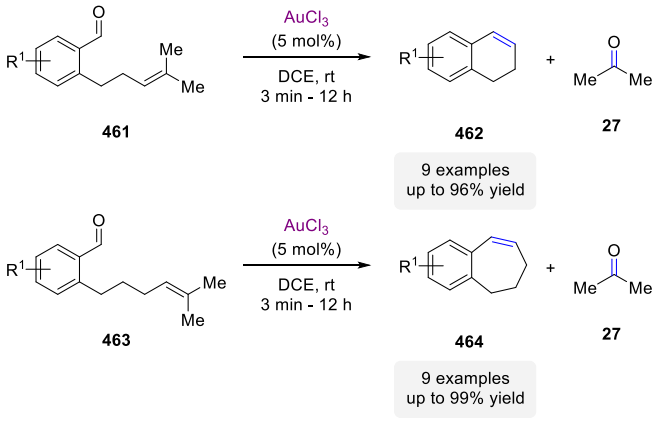
Scheme 78. Al(III)-Ion Pairs Promote Carbonyl-Olefin Metathesis *via* a Distinct Reaction Path by Schindler and Coworkers



During their initial reaction optimization of carbonyl-olefin ring-closing metathesis relying on Al(III)-ion pairs, Schindler and coworkers noticed the initial build-up and subsequent depletion of an intermediate. Subsequent efforts to isolate this intermediate identified it as unsaturated alcohol **457** and the product of a carbonyl-ene reaction, which when resubjected to the optimal reaction conditions resulted in the formation of the desired carbonyl-olefin metathesis product **456** (Scheme 78). Ensuing mechanistic investigations relying on ^{1}H-NMR, deuterium-labeling, and computational studies led Schindler and coworkers to postulate a distinct reaction pathway for Al(III)-catalyzed carbonyl-olefin ring-closing metathesis reactions resulting in 6-membered rings based on Lewis acid-activation of aryl ketone **451** to form Lewis acid-base complex **452**. A subsequent reversible carbonyl-ene reaction forms unsaturated alcohol **457**, which upon Lewis acid-catalyzed hydroalkoxylation gives rise to oxetane **454**. A final retro [2+2]-cycloaddition results in the formation of cyclohexene **456** and acetone **27** as the carbonyl-olefin metathesis products. This reaction pathway was found to be 3.3 kcal/mol lower in energy when comparing the reversible carbonyl-ene step to a [2+2]-cycloaddition reaction of Lewis acid-base complex **452** resulting directly in oxetane **454**. Nevertheless, substrates incapable of undergoing carbonyl-ene reactions including styrenyl alkene **459** forms cyclohexene **460** as the desired carbonyl-olefin metathesis

product under the optimal reaction conditions *via* [2+2]-cycloaddition and retro [2+2]-cycloaddition albeit in diminished yields of 44%. Notably, mechanistic data obtained in carbonyl-olefin metathesis reactions resulting in 5-membered ring systems supports a distinct reaction pathway that does not rely on a reversible carbonyl-ene reaction. Consequently, a carbonyl-ene step and a subsequent hydroalkoxylation is exclusive to carbonyl-olefin metathesis reactions resulting in 6-membered ring products.

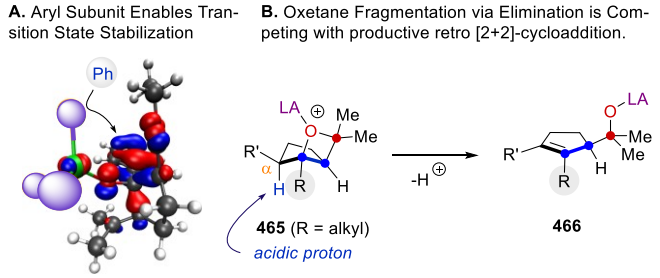
Scheme 79. Au(III)-Catalyzed Carbonyl-Olefin Ring-Closing Metathesis for the Formation of 6- and 7-Membered Rings by Lin and Coworkers



In 2019, Lin and coworkers reported that their reaction conditions relying on 5 mol% $AuCl_3$ as Lewis acid in dichloroethane at ambient temperatures were equally capable of resulting in the formation of 6-membered 1,2-dihydronapthalenes bearing distinct substitution in up to 96% yield (Scheme 79).[115] Furthermore, Lin and coworkers also reported the successful formation of their 7-membered ring analogs as functionalized 6,7-dihydro-5H-benzo[7]annulenes as demonstrated in seven examples and up to 99% yield.

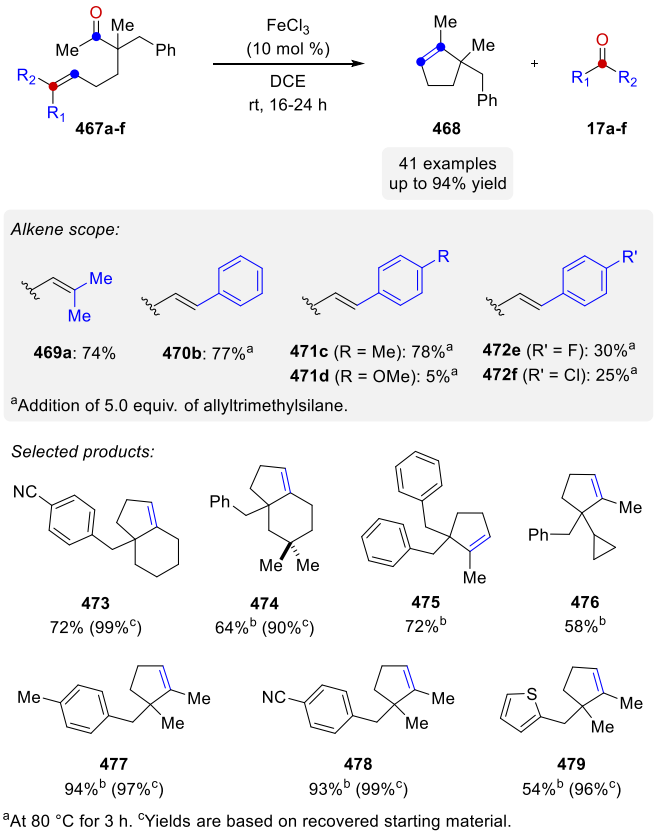
6.3 Catalytic Carbonyl-Olefin Ring-Closing Metathesis of Aliphatic Ketones

Scheme 80. Challenges in Lewis Acid-Catalyzed Carbonyl-Olefin Metathesis Reactions of Aliphatic Ketones



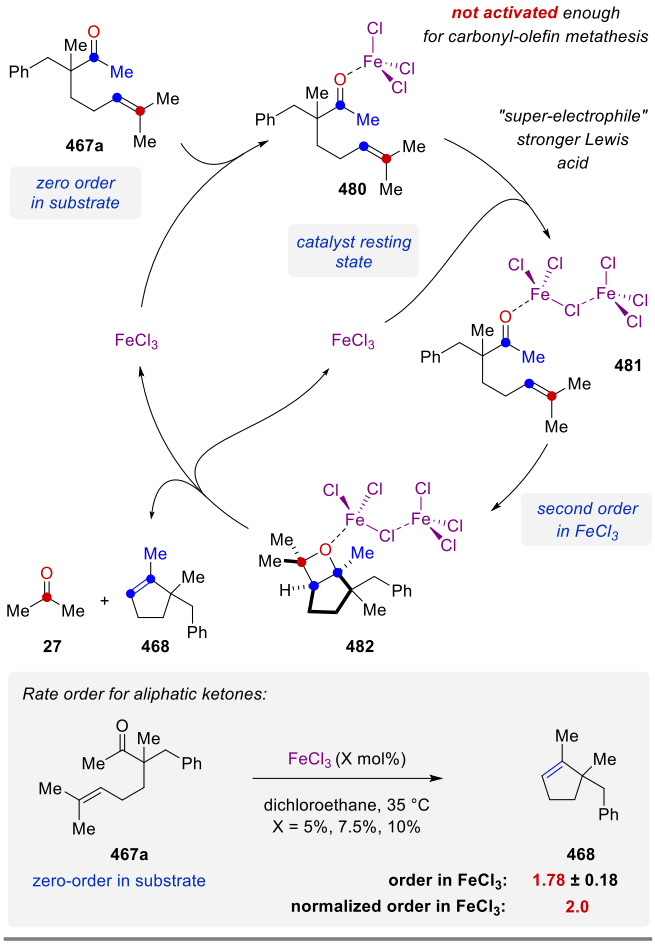
In comparison to catalytic carbonyl-olefin metathesis reactions of aryl ketones, those efficiently converting aliphatic ketones remain far less advanced. Currently, aliphatic ketone substrates bearing quaternary carbon centers in α-position to the carbonyl moiety undergo efficient carbonyl-olefin metathesis reaction to form cyclopentene products.[126] Importantly, aliphatic ketones face several challenges compared to their aromatic analogs that hamper their efficient conversion in carbonyl-olefin metathesis reactions (Scheme 80). Specifically, the aromatic moiety of aryl ketones redistributes electron density and thus aides in transition state stabilization (Scheme 80A). Additionally, alternative oxetane fragmentation pathways exist in which acidic protons in the oxetane intermediate can undergo undesired elimination reactions to result in unsaturated alcohols **466** (Scheme 80B).

Scheme 81. Carbonyl-Olefin Metathesis of Aliphatic Ketones by Schindler and Coworkers



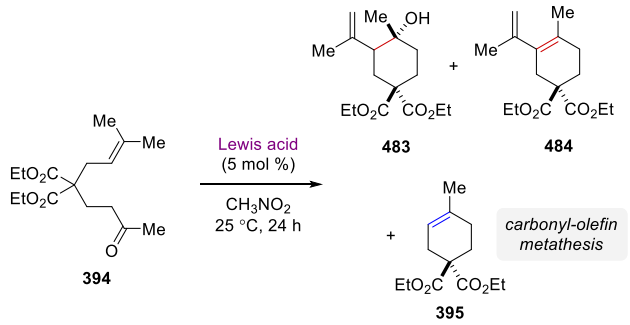
Due to these challenges, the first protocol for catalytic carbonyl-olefin metathesis of aliphatic ketones was not developed until early 2019 by the Schindler group.[126] The majority of substrates undergoing the desired transformation incorporate α-quaternary centers while the generality of this reaction protocol is demonstrated in 41 examples proceeding in up to 91% yield (Scheme 81). Prenylated alkenes prove superior compared to their styrenyl analogs, which require the addition of 5.0 equivalents of allyltrimethylsilane as reported in Li's protocol for $FeCl_3$-catalyzed carbonyl-olefin metathesis for the formation of 3-aryl-2,5-dihydropyrroles.[106] This difference in reactivity is most likely a direct consequence of the metathesis byproducts formed; while acetone can compete with the aliphatic ketone substrates for binding to the $FeCl_3$-catalyst, aromatic aldehyde byproducts are expected to be stronger binders than the corresponding substrates, thus leading to competing catalyst sequestration. Interestingly, the optimal reaction conditions identified require 10 mol% of $FeCl_3$ and prove limited to dichloroethane as reaction solvent while previous examples of catalytic carbonyl-olefin metathesis reactions proceeded efficiently in dichloromethane, toluene, and dichloroethane.[99] Additionally, kinetic studies of aliphatic ketone **467** subsequently conducted revealed a second-order dependence in $FeCl_3$ for carbonyl-olefin metathesis reactions of aliphatic ketones resulting in cyclopentene **468** while those relying on aryl ketone substrates show a first-order dependence in $FeCl_3$. The authors followed up their kinetic investigations with spectroscopic and computational investigations, which are consistent with a distinct activation mode for catalytic carbonyl-olefin metathesis reactions of aliphatic ketones resulting forming cyclopentenes (Scheme 81).

Scheme 82. $FeCl_3$-Homodimers as Active Catalytic Species in the Carbonyl-Olefin Metathesis of Aliphatic Ketones as Proposed by Schindler and Coworkers



Specifically, aliphatic ketone **467a** coordinates to $FeCl_3$ as the Lewis acid catalyst to form Lewis acid-base complex **480** as the catalyst resting state. In comparison to aryl ketones, this coordination complex is not sufficiently activated for carbonyl-olefin metathesis until a second equivalent of $FeCl_3$ binds to form a Lewis acidic "superelectrophile" in the form of a $FeCl_3$ singly-bridged homo-dimer **481**. This homodimer is a stronger Lewis acid compared to the individual Lewis acid monomers and thus capable of activating less reactive substrates. This mechanistic hypothesis aligns with literature reports[123-125] from over 60 years ago of superelectrophiles that were proposed to act as stronger Lewis acids in the form of homobimetallic dimers or ion pairs. The "superelectrophilic" Lewis acid-base complex **481** is now sufficiently activated to undergo the desired carbonyl-olefin ring-closing metathesis reaction *via* [2+2]-cycloaddition to form intermediate oxetane **482** and subsequent retro [2+2]-cycloaddition to ultimately give rise to the metathesis products cyclopentene **468** and acetone **27**. Recently, the singly-bridged $FeCl_3$ dimer has been investigated computationally by Zhu and coworkers in their studies of the carbonyl-olefin metathesis reactions to form aromatic species.[127]

Scheme 83. Lewis Acid-Catalyzed Intramolecular Carbonyl-Ene Reactions Reported by Duñach and Coworkers

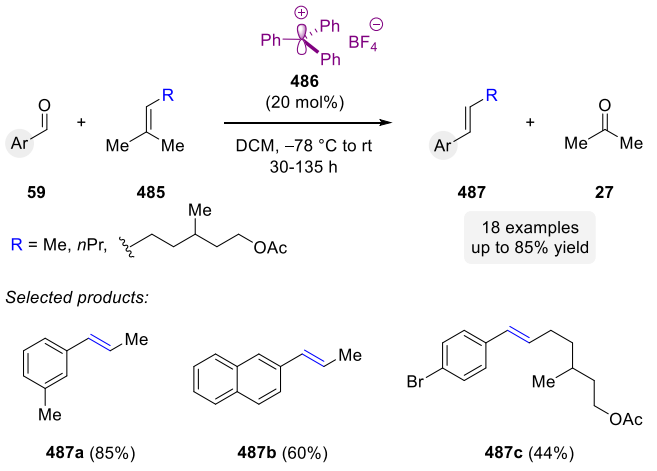


entry	Lewis acid	combined yield (%)	ratio **483**:**484**:**395**		
1	$Bi(OTf)_3$	32	41	50	9
2	$In(OTf)_3$	43	60	33	7
3	$Fe(OTf)_3$	29	97	3	0
4	$In(NTf_2)_3$	58	7	62	31
5	$Fe(NTf_2)_2$	34	0	26	74

During their studies of intramolecular carbonyl-ene reactions of aliphatic ketone **394**, Duñach and coworkers reported evidence of the carbonyl-olefin metathesis product in the investigations of catalytic, intramolecular carbonyl-ene reaction of aliphatic that in addition to the carbonyl-ene product **483** and its dehydrated analog **484**, cyclohexene **395** was formed as the carbonyl-olefin metathesis product.[119] In the presence of $Bi(OTf)_3$, acting as the Lewis acid catalyst, **394** undergoes the carbonyl-ene reaction to provide *cis* and *trans* carbonyl-ene products **483**, the elimination product **484** and the metathesis product **395** in a combined yield of 32% and a 41:50:5 ratio (Scheme 83). Interestingly, the use of $In(NTf_2)_3$ and $Fe(NTf_2)_2$ as the Lewis acid catalyst increased the ratio of the carbonyl-olefin metathesis product. Notably, diene **484** and cyclohexene **395** were formed as the exclusive products in a combined yield of 34% and a 26:74 ratio when relying on catalytic amounts of $Fe(NTf_2)_2$ in nitromethane at ambient temperatures for 24 hours. The authors suggest that cyclohexene **395** arises from an intramolecular hydroalkoxylation onto carbonyl-ene product and subsequent fragmentation.

6.4. Catalytic Cross Carbonyl-Olefin Metathesis

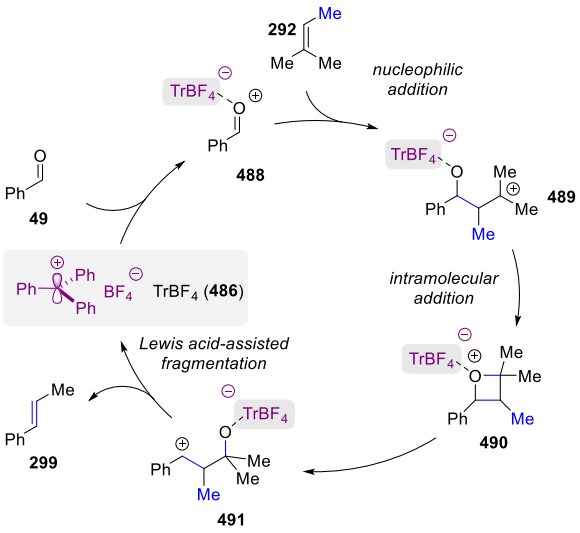
Scheme 84. *E*-Selective Cross-Metathesis by Franzén and Coworkers



In 2015, Franzén and coworkers built on the studies originally published by Bickelhaupt and coworkers[95] in 1994 to realize a cross carbonyl-olefin metathesis reaction between benzaldehyde **59** and isobutylene **485** by incorporating important modifications to the procedure. Specifically, the Franzén group had previously identified trityl tetrafluoroborate (**486**, $TrBF_4$) as a Lewis acid capable

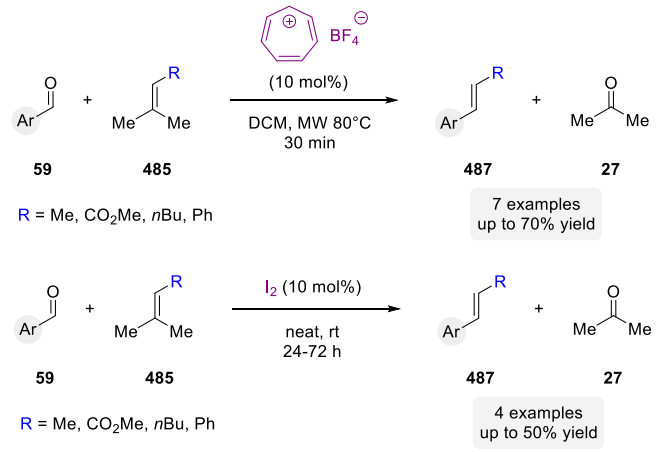
of catalyzing a variety of organic transformations, including Diels-Alder and conjugate addition reactions.[128] In an initial reaction, an equimolar ratio of benzaldehyde and amylene was converted with 7 mol% $TrBF_4$ (**486**) to result in 20% yield of the desired cross carbonyl-olefin metathesis product. Subsequent reaction optimization revealed that a 5:1 ratio of aryl aldehyde to alkene with 20 mol% $TrBF_4$ (**486**) proved optimal and gave rise to the desired cross carbonyl-olefin metathesis products in up to 85% yield (Scheme 84). Additionally, conducting the transformation at lower temperatures albeit for longer reaction times resulted in decreased competing polymerization and catalyst decomposition.

Scheme 85. Mechanistic Hypothesis for Catalytic Cross Carbonyl-Olefin Metathesis



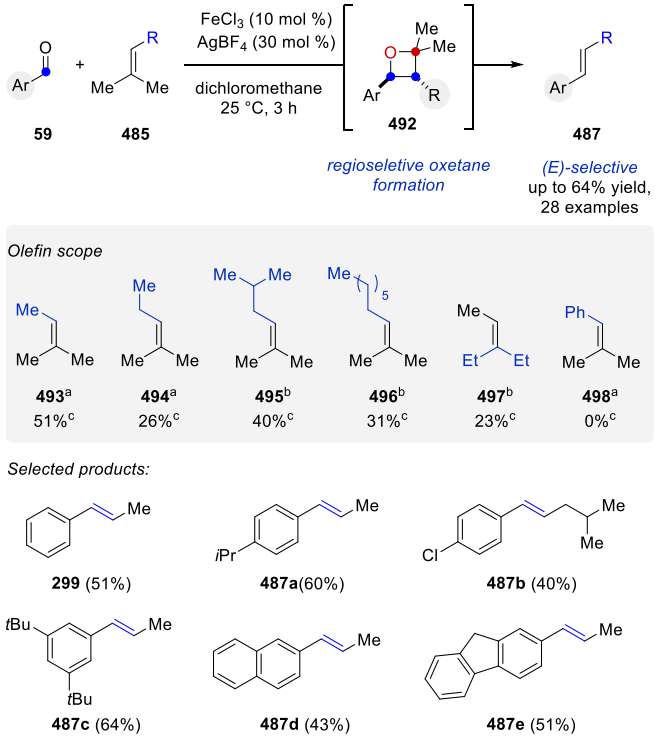
Following the initial mechanistic hypothesis proposed by Bickelhaupt for a Lewis acid-mediated cross carbonyl-olefin metathesis, Franzén and coworkers suggest a similar proposal that relies on initial LUMO activation of aldehyde **59** by $TrBF_4$ (**486**) as the Lewis acid catalyst. Nucleophilic addition of alkene **292** onto the Lewis acid-base complex **488** results in carbon-carbon bond formation in carbocation **489** (Scheme 85). Intramolecular addition of the oxygen onto the carbocation forms oxetane **490**, which undergoes subsequent C-O bond fragmentation to form benzylic carbocation **491**. A final Lewis acid-assisted fragmentation gives rise to alkene **299** and acetone as the cross carbonyl-olefin metathesis products and $TrBF_4$ (**486**) as the Lewis acid catalyst. Although this mechanistic hypothesis is not supported by experimental investigations, it is based on the known reactivity between carbonyl and alkene functionalities undergoing Prins-cyclizations[129] to form **491**, which then undergoes a subsequent intramolecular, nucleophilic addition.

Scheme 86. Tropylium-Ions and Iodine as Lewis Acid Catalysts in Intermolecular Carbonyl-Olefin Cross Metathesis Reactions by Nguyen and Coworkers



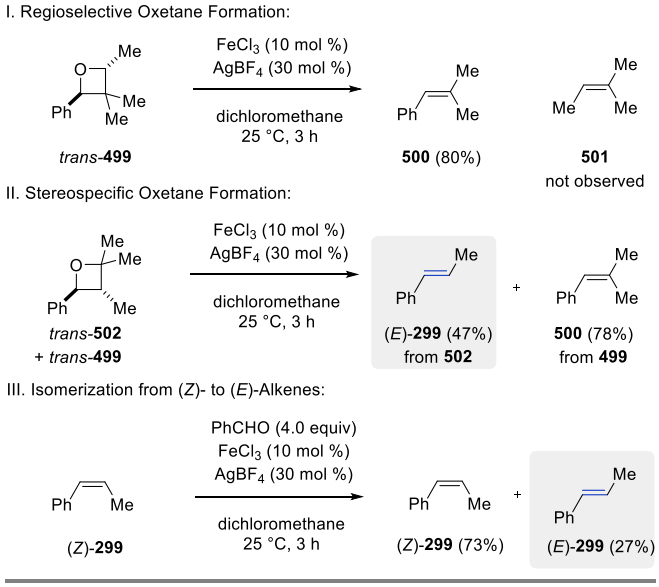
In 2018, Nguyen and coworkers showed that catalytic amounts of tropylium tetrafluoroborate (10 mol%) as Lewis acid is similarly capable of promoting the cross carbonyl-olefin metathesis reaction (Scheme 86).[113] The optimal reaction conditions also require an excess of aldehyde compared to the alkene substrate (5:1 ratio of aldehyde to alkene) in dichloromethane at 80 °C under microwave irradiation for 30 minutes to form the metathesis products in up to 70% yield. The authors conducted additional mechanistic investigations based on DFT studies, which support a stepwise reaction pathway for intermolecular carbonyl-olefin cross-metathesis reactions similar to that suggested by Franzén and coworkers, in which stepwise oxetane formation and fragmentation are essential components of the reaction pathway. In 2019, Nguyen and coworkers followed up on this report and showed that molecular iodine (10 mol%) also functioned as a suitable Lewis acid to catalyze this transformation.[114] Notably, optimal reaction conditions proceed at ambient temperatures with a 2:1 ratio of aldehyde to alkene resulting in the metathesis products in up to 50% yield in reaction times of one to three days (Scheme 86).

Scheme 87. *E*-Selective Intermolecular Carbonyl-Olefin Metathesis by Schindler and Coworkers



The Schindler lab reported a cross carbonyl-olefin metathesis reaction protocol in 2020 relying on Fe(III)-ion pairs as superelectrophilic Lewis acid catalysts.[130] Similarly to previous reports by Franzén[128] and Nguyen,[113,114] this approach is exclusive to aryl aldehydes and relies on an excess of the carbonyl component in a 5:1 ratio compared to the alkene substrate. Nevertheless, the reaction proceeds in dichloromethane as optimal solvent at ambient temperatures within three hours to result in the formation of the desired cross carbonyl-olefin metathesis products in up to 64% yield. An investigation of the alkene scope of this transformation (Scheme 87) revealed that tri-alkylsubstituted alkenes performed best, which is consistent with previous literature reports.

Scheme 88. *E*-Selectivity due to Regioselective Oxetane Formation



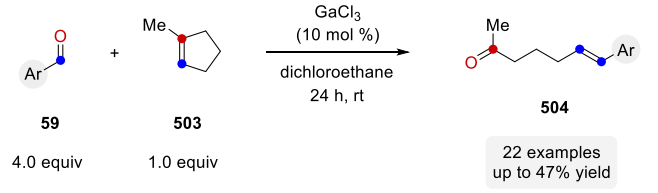
As part of these studies, the origin of the high (*E*)-selectivity of catalytic cross carbonyl-olefin metathesis reactions was investigated (Scheme 88). Importantly, four distinct oxetane stereoisomers could form upon addition of the aldehyde and alkene substrates, which could fragment to form three distinct alkene products. The Schindler group independently synthesized oxetane *trans*-**499** and showed that it results in the selective formation of alkene in 80% while alkene **501**, the product obtained in cross carbonyl-olefin metathesis reactions, was not observed. A mixture of *trans*-**502** and *trans*-**499** in a ratio of 1:1.26 resulted in (*E*)-**299** in 47% yield (from *trans*-**594**) and **592** in 78% yield (based on *trans*-**593**) while no formation of the (*Z*)-isomer of (*E*)-**299** was observed. A final set of experiments investigated the ability of (*Z*)-**299** to isomerize to (*E*)-**299** under the optimal reaction conditions. While isomerization from (*Z*)- to (*E*)-**299** is feasible under these conditions, it was determined unlikely to be responsible for the formation of (*E*)-**299** as the exclusive product on the timescale of this transformation. Collectively, these results are consistent with the regioselective formation of a single oxetane intermediate and its subsequent stereospecific fragmentation in the course of cross carbonyl-olefin metathesis reactions to account for the selective formation of (*E*)-alkene products.

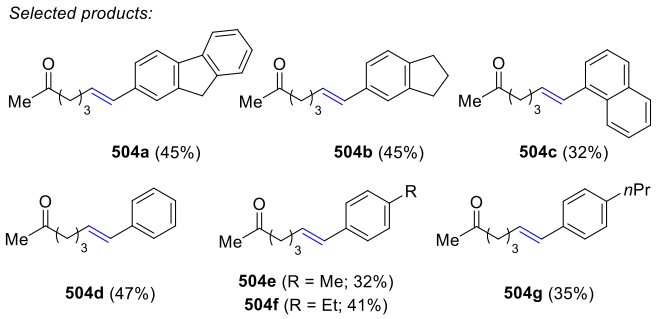
A further investigation into the mass balance of this reaction determined a competing reaction pathway for the oligomerization of the starting materials to account for the low overall yields observed in catalytic cross carbonyl-olefin metathesis reactions. Similar observations of a polymeric byproduct had previously been reported by Franzén and coworkers.[128]

Although cross carbonyl-olefin metathesis reactions hold great potential for the catalytic synthesis of new alkene products, they arguably remain among the least advanced classes of this transformations. Importantly, substrates are currently limited to aryl aldehydes and trisubstituted aliphatic alkenes and require a large excess of 5 equivalents of the carbonyl component to proceed. Although progress has been made understanding the exclusive (*E*)-selectivity of these transformations, the reaction mechanism in addition to the origin of polymeric byproducts remains poorly understood and will require further careful investigations.

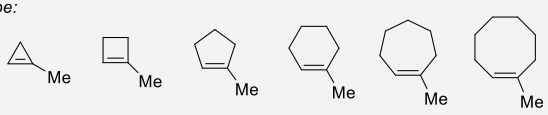
6.5. Catalytic Carbonyl-Olefin Ring-Opening Metathesis

Scheme 89. Ring-Opening Carbonyl-Olefin Metathesis by Schindler and Coworkers





Alkene scope:

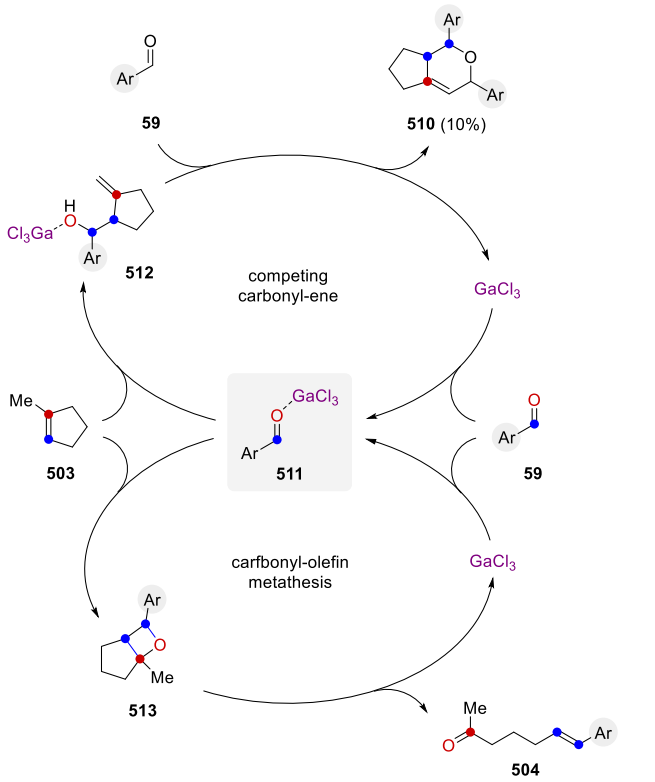


	505	506	503	507	508	509
RSE[a]	54.5	29.7	5.0	1.7	6.3	7.4
reactivity	0%	-	47%	18%	0%	0%

[a]Ring strain energy (kcal/mol).

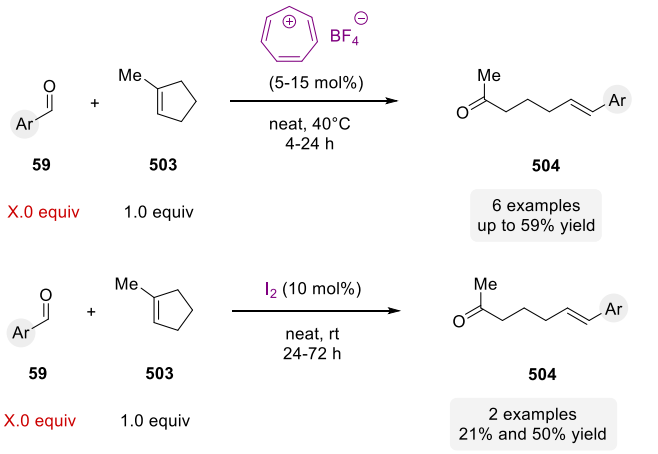
In 2018, the first reports of Lewis acid-catalyzed carbonyl-olefin ring-opening metathesis were published by the laboratories of Nguyen and Schindler. The reaction protocol reported by Schindler and coworkers relies on catalytic amounts of $GaCl_3$ as the superior Lewis acid catalyst compared to $FeCl_3$, which also resulted in accompanying decomposition of the metathesis products formed.[131] The generality of this approach was demonstrated for a range of 22 examples accessible in up to 47% yield from aryl aldehyde and cyclic alkene substrates (Scheme 89). The initial hypothesis that the ability of cyclic alkenes to undergo carbonyl-olefin ring-opening metathesis was directly related to their inherent ring strain did not prove viable as cyclopentene **503** and cyclohexene **507** underwent the desired transformation in 47% and 18% yield, respectively, while cycloheptene **508** exhibiting a higher ring strain compared to **503** and **507** resulted in no formation of the carbonyl-olefin metathesis products.

Scheme 90. Carbonyl-Olefin Metathesis and Carbonyl-Ene Reaction Paths Compete in Catalytic Ring-Opening Reactions as Proposed by Schindler and Coworkers



Subsequent efforts conducted by Schindler and coworkers focused on investigations related to the overall mass balance of this transformation, which provided at best 47% yield of the desired carbonyl-olefin ring-closing metathesis products (Scheme 90). ^{1}H-NMR studies led to the isolation and subsequent characterization of two additional products formed, specifically cyclic ether **510** formed in 10% yield and bisalkene **514** obtained in 20% yield. The authors hypothesized that both undesired byproducts are formed in a competing carbonyl-ene reaction and subsequent addition of either a second equivalent of aryl aldehyde **59** or cyclopentene **503** to the carbonyl-ene intermediate. Consequently, $GaCl_3$-catalyzed carbonyl-olefin ring-closing metathesis reactions proceed upon coordination of the Lewis acid catalyzed to the aryl aldehyde **59** to form Lewis acid-base complex **511**, which can undergo a subsequent [2+2]-cycloaddition with cyclopentene **503** to result in intermediate oxetane **513**. A final fragmentation of oxetane **513** *via* retro [2+2]-cycloaddition gives rise to unsaturated ketone **504** as the desired carbonyl-olefin ring-opening metathesis product. Alternatively, Lewis acid-base complex **511** can undergo a competing carbonyl-ene reaction upon carbon-carbon bond formation with cyclopentene **503** to result in unsaturated alcohol **512**. This intermediate can undergo two distinct addition reactions upon dehydration with either aryl aldehyde **59** or cyclopentene **503** to form cyclic ether **510** or bisalkene **514** as competing byproducts responsible for the overall diminished yields observed in carbonyl-olefin ring-closing metathesis.

Scheme 91. Tropylium-Ions and Iodine as Lewis Acid Catalysts in Intermolecular Carbonyl-Olefin Ring-Opening Metathesis Reactions by Nguyen and Coworkers



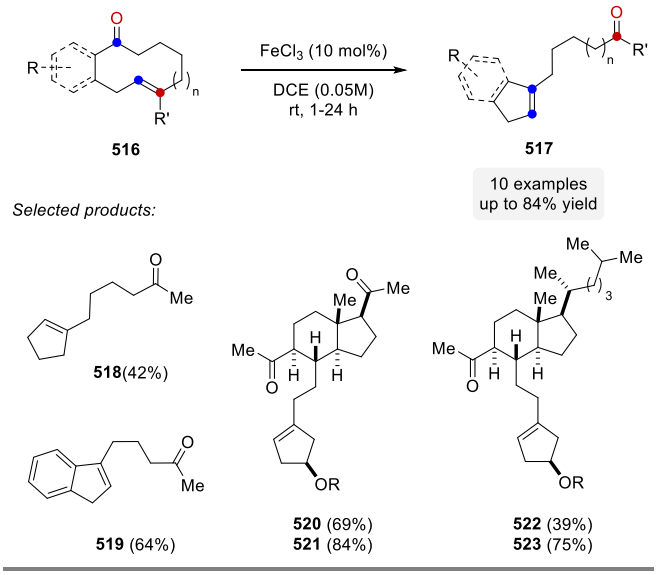
Similar observations were reported in 2018 by Nguyen and coworkers in their studies of tropylium tetrafluoroborate-catalyzed carbonyl-olefin ring-opening metathesis reactions.[113] The optimized conditions rely on 5 mol% of the Lewis acid catalyst, neat, at 40 °C for up to 24 hours and result in up to 59% yield for a range of 6 examples (Scheme 91). Notably, cyclopentenes were identified as the optimal alkene component while larger ring systems failed to provide the desired metathesis products.

In 2019, Nguyen and coworkers followed up on this report and showed that molecular iodine (10 mol%) was similarly capable of catalyzing carbonyl-olefin ring-opening metathesis reactions as demonstrated for two examples proceeding in up to 50% yield (Scheme 91).[114]

Together with carbonyl-olefin cross metathesis reactions, carbonyl-olefin ring-opening metathesis reactions currently remain among the least advanced. 5-Membered cyclic alkenes represent the most viable substrate class with respect to the alkene component, while their 6-membered ring analogs result in significantly diminished yields and higher order ring systems fail to undergo the desired transformation. With regard to the carbonyl substrate, ring-opening metathesis reactions are limited to aryl aldehydes while ketones and aliphatic aldehydes do not undergo carbonyl-olefin ring-opening metathesis. The lower overall yields observed in these transformations of ~50% can be attributed to competing carbonyl-ene reaction pathways that lead to reactive intermediates capable of undergoing subsequent addition reactions with the aryl aldehyde or cyclic alkene substrates.

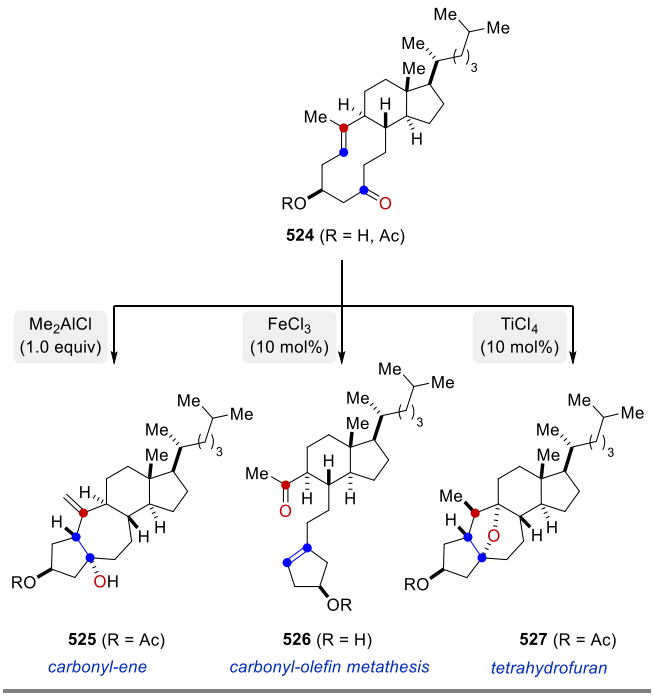
6.6. Catalytic Transannular Carbonyl-Olefin Metathesis

Scheme 92. Catalytic, Transannular Carbonyl-Olefin Metathesis by Schindler and Coworkers



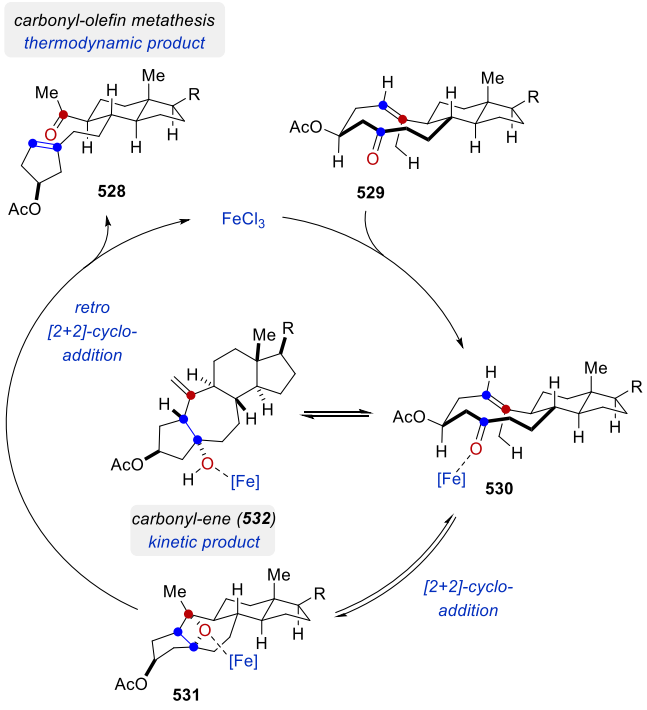
In 2019, the Schindler laboratory reported a catalytic, transannular carbonyl-olefin metathesis reaction relying on $FeCl_3$ as the Lewis acid catalyst and cyclic, unsaturated ketones **516** as substrates (Scheme 92).[27] The development of this transformation was inspired by earlier reports of Khripach and coworkers in 2006 who observed a ring-opening and subsequent ring-contraction during their studies towards the synthesis of steroid frameworks mediated by $BF_3 \cdot OEt_2$.[97] During their reaction optimization, Schindler and coworkers were able to show that catalytic amounts of $FeCl_3$ were capable to catalyze transannular carbonyl-olefin metathesis reactions of 9- and 10-membered ring systems (**516**) incorporating carbonyl and alkene moieties. The scope of this transformation was demonstrated in 10 examples resulting in up to 84% yield of the desired carbonyl-olefin metathesis products **518-523**.

Scheme 93. Divergent Reactivity in Transannular Reactions of Unsaturated, Cyclic Ketones **524** with Me_2AlC, $FeCl_3$, or $TiCl_4$ as Lewis Acid



Interestingly, initial studies with unsaturated, cyclic ketone **524** aimed at the optimization of this transformation with distinct Lewis acids, including Me_2AlCl, $FeCl_3$, and $TiCl_4$ resulted in the formation of three distinct products, specifically carbonyl-ene product **525** when using equimolar amounts of Me_2AlCl, carbonyl-olefin metathesis product **526** with catalytic amounts of $FeCl_3$, and tetrahydrofuran **527** with catalytic amounts of $TiCl_4$ (Scheme 93). This divergent reactivity proved general for a variety of 9- and 10-membered ring substrates and prompted additional mechanistic investigations by Schindler and coworkers. Based on these efforts, the authors postulate a mechanistic hypothesis for transannular carbonyl-olefin metathesis in which the substrate **529** binds to $FeCl_3$ as the Lewis acid to form Lewis acid-base complex **530**. This complex can undergo either of two reversible transformations, specifically a carbonyl-ene reaction resulting in unsaturated alcohol **532** as the kinetic product or a reversible asynchronous, concerted [2+2]-cycloaddition to form oxetane **531** as the thermodynamic product. Experimental studies support this hypothesis as the kinetic product **532** can be isolated at lower reaction temperatures as a stable product. Oxetane **531** subsequently undergoes $FeCl_3$-catalyzed retro-[2+2]-cycloaddition to result in the formation of **528** as the product of a transannular carbonyl-olefin metathesis reaction (Scheme 94). When cyclodecenone **524** is converted with stoichiometric amounts of Me_2AlCl as Lewis acid, the carbonyl-ene reaction path is not reversible as **526** is isolated exclusively as the thermodynamic product. Interestingly, the formation of tetrahydrofuran products **527** has not previously been observed under conditions promoting carbonyl-olefin metathesis reactions. The authors suggest that under $TiCl_4$-catalyzed conditions, oxetane **531** undergoes competing oxetane fragmentation *via* elimination to form an intermediate unsaturated alcohol capable of undergoing subsequent hydroalkoxylation onto the alkene moiety to result in the formation of tetrahydrofuran **527**.

Scheme 94. Mechanistic Hypothesis for Catalytic, Transannular Carbonyl-Olefin Metathesis by Schindler and Coworkers



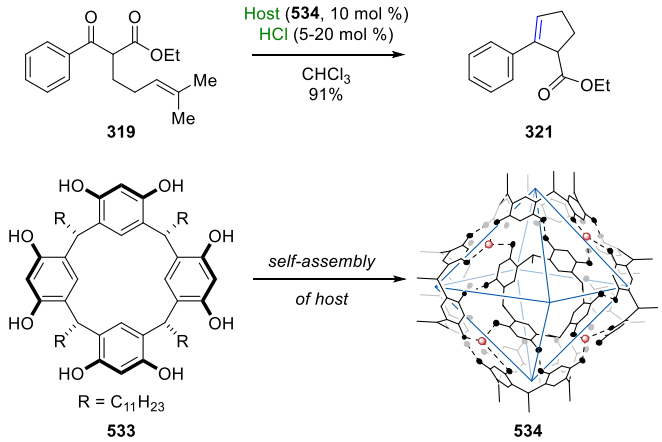
Lewis acids have proven to be exceptional catalysts for carbonyl-olefin metathesis. Since the first discoveries relying on stoichiometric amounts of a Lewis acid, a diverse array of catalytic systems has been reported to promote ring-closing, ring-opening, cross, and transannular carbonyl-olefin metathesis reactions. Detailed mechanistic studies have been conducted which suggest that the overall reaction pathway is substrate-dependent, relying on either concerted cyclization and fragmentation, carbonyl-ene products as reactive intermediates, or step-wise sequences. Importantly, while the carbonyl-ene pathway was shown

to be productive for metathesis in some instances, it can also lead to detrimental byproduct formation in others. Catalytic amounts of $FeCl_3$ has been established as a superior catalytic system for many substrates undergoing ring-closing carbonyl-olefin metathesis. Nevertheless, many other Lewis acids will show reactivity in these transformations albeit often leading to diminished yields of the desired products. Recently, the development of new catalyst systems relying on superelectrophilic Lewis acids significantly broadened to scope of Lewis acid-catalyzed carbonyl-olefin metathesis reactions. However, further advances are necessary to establish carbonyl-olefin metathesis as a general synthetic strategy for alkene synthesis.

7. OTHER CARBONYL–OLEFIN METATHESIS STRATEGIES

7.1 Ring-Closing Carbonyl-Olefin Metathesis

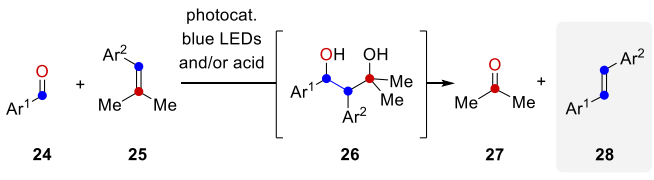
Scheme 95. Brønsted Acid-Catalyzed Metathesis in a Self-Assembled Supramolecular Host by Tiefenbacher



In 2018, Catti and Tiefenbacher[132] showed that HCl as a Brønsted acid in combination with a self-assembled host[133,134] was able to promote intramolecular ring-closing metathesis of a variety of previously established aryl ketone substrates **319** in moderate to good yields (Scheme 95). Supramolecular hosts have been increasingly investigated for their ability to facilitate reactions that are difficult to perform in bulk solution. One of the most commonly studied host systems, resorcin[4]arene hexamer (**534**), [135-139] spontaneously self-assembles in apolar solvents like chloroform *via* hydrogen bonding. Hexamer **534** is proposed to stabilize cationic transition states through cation-π interactions with the aromatic cavity walls.[140] Following optimization, the general conditions were determined to be 10 mol% of the self-assembled host and 5-20 mol% of HCl in $CHCl_3$ at 50 °C for 1-8 days. This report suggests that the supramolecular host and the Brønsted acid work synergistically to catalyze the metathesis reaction inside the cavity of the host structure. Initial mechanistic experiments based on trapping studies suggest that the reaction undergoes a stepwise formation of the intermediate oxetane under optimized conditions.

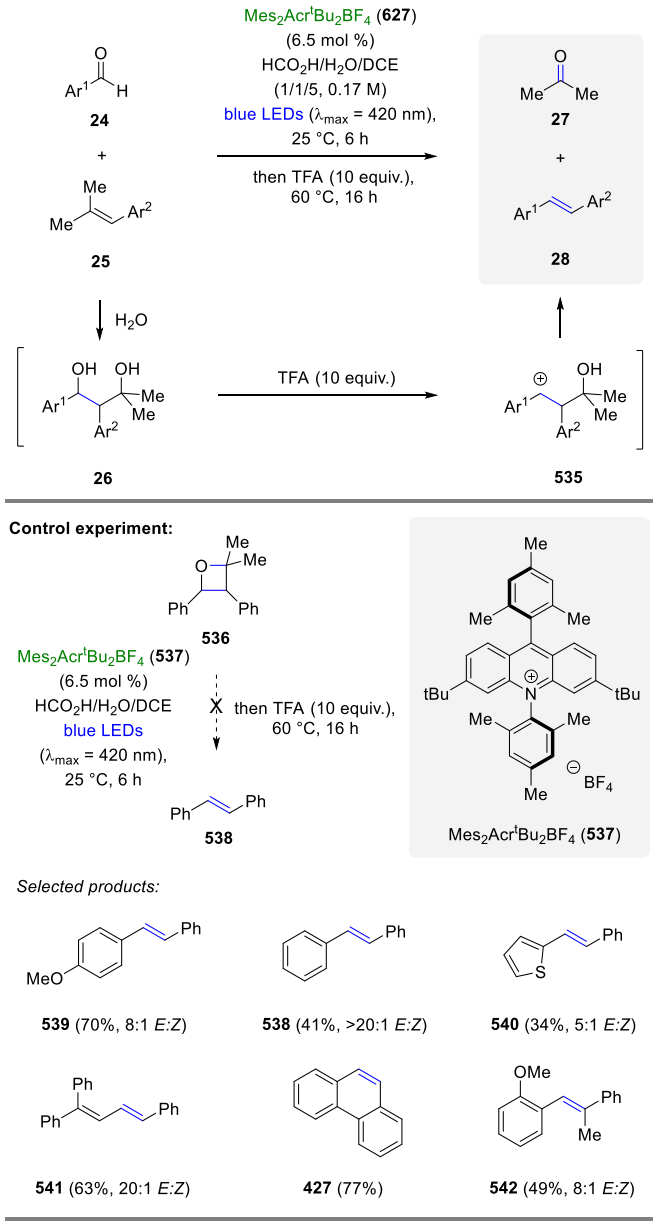
7.2 Cross Carbonyl-Olefin Metathesis

Scheme 96. Cross Carbonyl-Olefin Metathesis Relying on Grob Fragmentations



An alternative catalytic strategy developed for cross carbonyl-olefin metathesis reactions takes advantage of a two-step reaction sequence that can be conducted *in situ* that relies on initial carbon-carbon bond formation and subsequent Grob fragmentations (Scheme 96). This reaction design principle is currently limited to the formation of styrene derivatives **28** as the Grob Fragmentation requires the formation of stabilized carbocations. Consequently aryl aldehydes have proven superior as substrates following this strategy for catalytic cross carbonyl-olefin metathesis.

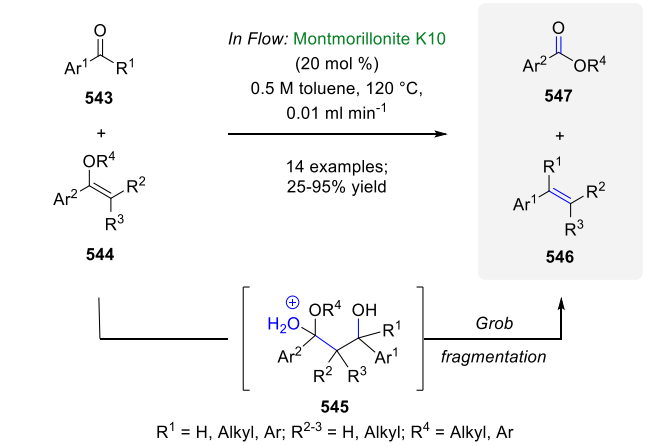
Scheme 97. Carbonyl–Olefin Cross-Metathesis *via* Visible-Light-Induced 1,3-Diol Formation and Fragmentation Sequence by Glorius



The Glorius group reported an intermolecular cross carbonyl-olefin metathesis protocol that employed a photocatalysis approach relying on $Mes_2Acr^tBu_2BF_4$ (**537**) in combination with Brønsted acids (Scheme 97).[141] Initial mechanistic investigations conducted by the authors are consistent with a stepwise reaction path that proceeds *via* carbon-carbon bond formation between aryl aldehyde **24** and olefin **25** to form diol **26** under the aqueous reaction conditions. Subsequent loss of water upon activation of the benzylic

alcohol moiety with trifluoroacetic acid results in the formation of carbocation **535**, which undergoes Grob fragmentation to result in styrene derivatives **28** and acetone **27** as net carbonyl-olefin metathesis products. Control experiments focused on the conversion of oxetane **536** under the optimal reaction conditions, which failed to provide styrene **538**. In comparison, the diol accessible upon carbon-carbon bond formation between benzaldehyde and 2-methyl-1-phenyl-1-propene readily results in the formation of styrene and supports the hypothesis that oxetanes do not function as key intermediates in this transformation.[142,143] The reaction design proved general for the synthesis of a variety of styrenes (**539**-**542**) in good yields and diastereomeric ratios of >20:1.

Scheme 98. Intermolecular Carbonyl-Olefin Metathesis of Vinyl Ethers Catalyzed by Solid Acids in Flow by Leyva-Pérez



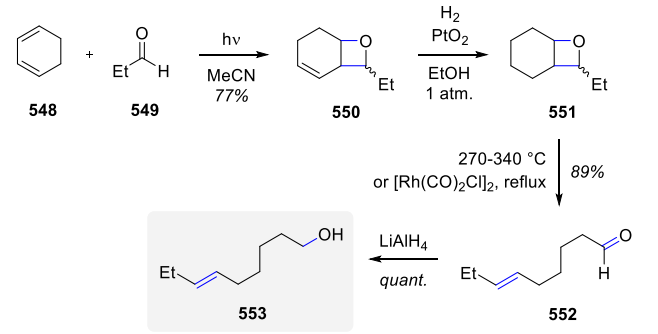
Following the report for carbonyl-olefin metathesis by Glorius and coworkers relying on a Grob fragmentation approach, a similar strategy was developed by Leyva-Pérez and coworkers to access styrene derivatives from aryl aldehydes and ketones (**543**) with vinyl ethers (**544**).[144] This approach utilized an inexpensive, non-toxic aluminosilicate montmorillonite solid-state acid catalyst, montmorillonite K10 (Scheme 98). Solid, fixed-bed acids allowed for the intermolecular carbonyl-olefin metathesis reaction to be conducted in-flow; avoiding unwanted side reactivity of vinyl ether hydrolysis. Computational and experimental results supported an acid-catalyzed mechanism that proceeds through hemiacetal **545** as a key intermediate, which then undergoes a dehydration to form a benzylic carbocation, followed by a subsequent Grob fragmentation to provide ester **547** along with styrene derivative **546** as the desired metathesis product. Notably, only the formation of the *E*-isomers is observed under the optimized reaction conditions for all substrates investigated.

In summary, these examples highlight the ability of Brønsted acids to promote carbonyl-olefin metathesis on a variety of substrate classes. The acidic environment promotes the formation of cationic intermediates which are able to successfully fragment to yield the desired olefin products. Additionally, these conditions were translated to a continuous flow platform resulting in comparable yields of the desired carbonyl-olefin metathesis products. In comparison to Lewis acid-catalyzed approaches, the development of Brønsted acid-catalyzed carbonyl-olefin metathesis reactions is less advanced currently following either the design principle of Lewis acid-catalyzed ring-closing reactions or a Grob fragmentation approach.

8. APPLICATIONS IN NATURAL PRODUCT SYNTHESIS

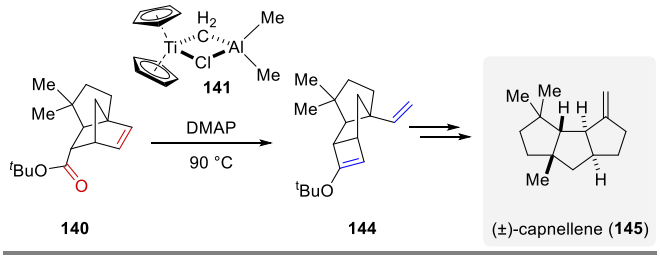
Carbonyl-olefin metathesis reactions have seen important applications in natural product synthesis, particularly approaches that enable ring-closing transformations. Interestingly, the majority of these applications in total synthesis relies on metal alkylidenes as stoichiometric reagents, which points towards the synthetic potential of carbonyl-olefin metathesis. Since the first strategies for catalytic carbonyl-olefin metathesis have been developed within the past decade, future applications of these reaction protocols in complex settings are to be expected, which will lead to the identification of existing limitations in catalytic carbonyl-olefin metathesis to ultimately spur further important advances in reaction development. This part of the review provides an overview of reported applications for carbonyl-olefin metathesis reactions in the synthesis of natural products since 1975.

Scheme 99. Synthesis of the Mediterranean Fruit Fly Pheromone *trans*-Non-6-en-1-ol by Jones



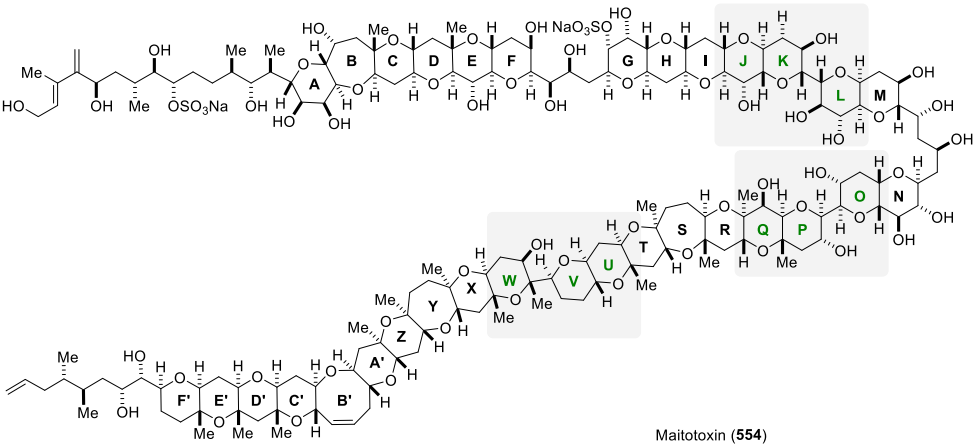
In 1975, Jones and coworkers developed a four-step synthetic sequence for the Mediterranean fruit fly pheromone *trans*-non-6-en-1-ol (**553**)[33] based on a carbonyl-olefin metathesis sequence that relies on initial photochemical [2+2]-cycloaddition and a subsequent Lewis acid-mediated cycloreversion[32] (Scheme 99). Paternò-Büchi reaction occurs upon photochemical irradiation with a 450W Hanovia immersion lamp between cyclohexa-1,3-diene **548** and propionaldehyde **549** resulted in the formation of oxetane **550** in 77% yield. Reduction of the internal alkene with PtO_2 gave rise to its reduced analog **551**, which undergoes a [2+2]-cycloreversion upon treatment with $[Rh(CO_2)Cl]_2$ as a Lewis acid under elevated temperatures to form aldehyde **552** in 89% yield. Final reduction of **552** with $LiAlH_4$ results in the quantitative formation of trans-non-6-en-1-ol (**553**).

Scheme 100. Synthesis of (±)-Capnellene by Grubbs and Stille

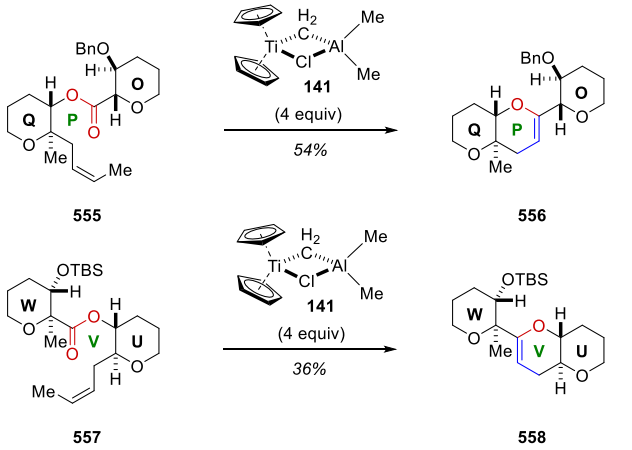


Grubbs and Stille published the first application of carbonyl-olefin metathesis towards the synthesis of capnellene in 1986[49,50] utilizing the Tebbe reagent.[56] Capnellene is a proposed precursor to the capnellene family of nonisoprenoid sesquiterpenes and possesses promising antibacterial and antitumor properties.[145,146] The approach developed by Grubbs and Stille utilizes a Diels-Alder reaction to form bicyclic **140**, which subsequently undergoes an intramolecular carbonyl-olefin ring-opening metathesis relying on stoichiometric amounts of Tebbe reagent to form the cyclobutene **144** in 84% yield (Scheme 100). This tricyclic intermediate was ultimately further advanced to provide the cis-anti-cis tricycle(6.3.0.0)undecane skeletal framework of capnellene **145**.

Scheme 101. Structure of Maitotoxin, a Natural Toxin Produced by *Gambierdiscus toxicus*

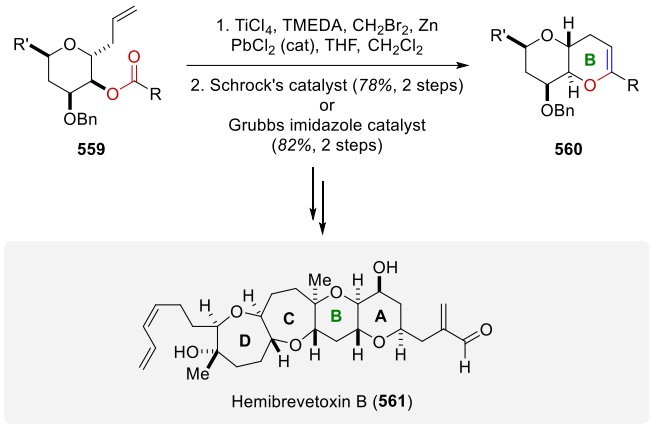


Scheme 102. Synthesis of Maitotoxin Subunits Relying on Carbonyl-Olefin Metathesis by Nicolaou and Coworkers



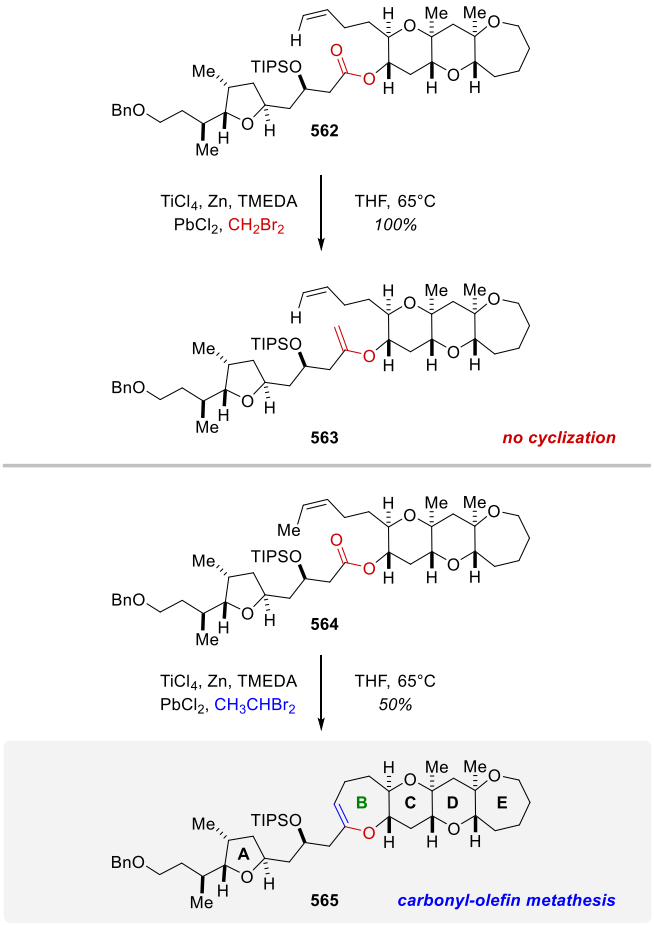
The structure the potent nonpeptidic toxin, maitotoxin **554**, was elucidated in 1996[147] and contains 32 ring systems, most of them fused consecutively, and 98 stereocenters (Scheme 101). Nicolaou and coworkers reported the construction of the JKL, OPQ, and UVW ring systems relying on carbonyl-olefin metathesis reactions mediated by the Tebbe reagent. Utilizing their previously reported reaction protocol[64] for the formation of cyclic enol ethers from olefin and ester moieties, the P-ring subunit was formed *via* carbonyl-olefin metathesis in 54% yield starting from ester **555** linking the Q- and O-rings (Scheme 102).[148] The V-ring was formed in an analogous manner in 36% yield proving that this this a powerful strategy for the rapid construction of the complex cyclic polyether framework common to maitotoxin and structurally related, smaller natural products.

Scheme 103. Strategy Towards Hemibrevetoxin B by Rainier and Coworkers



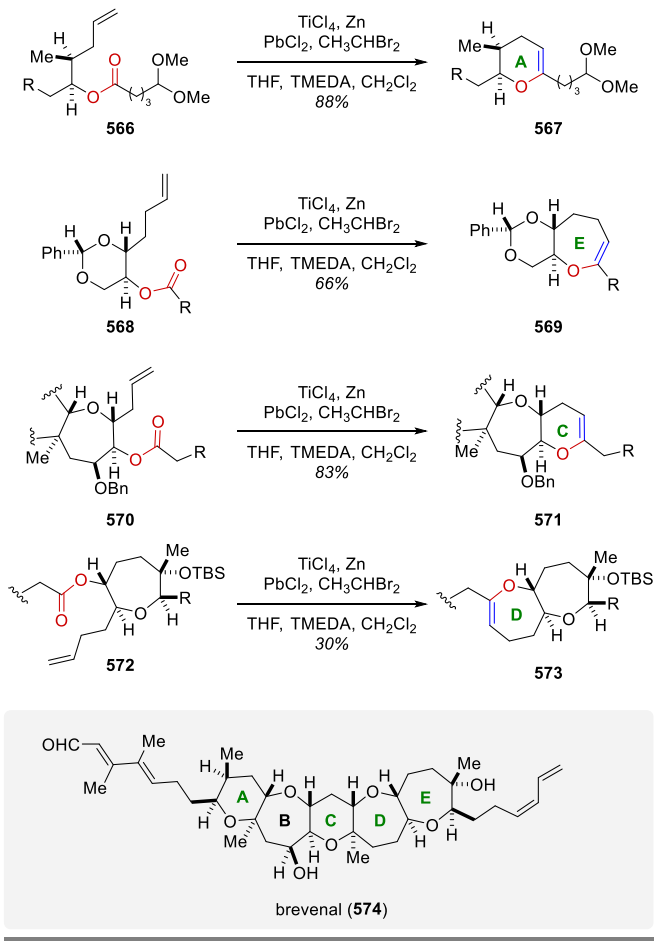
The marine ladder toxins possess highly complex structures and interesting biological properties, including neurotoxicity and antimicrobial properties.[149-153] Hemibrevetoxin B (**561**)[154] belongs to the marine ladder toxin family and consists of 4 heterocyclic rings and 10 stereocenters. Rainier and coworkers approached the synthesis of hemibrevetoxin B (**561**) based on a general strategy to enable the coupling of *C*-glycosides *via* carbonyl-olefin metathesis to form the spirocyclic subunit B (**560**).[155] Specifically, they relied on two-step approach previously developed in their laboratory[65] to first convert ester **559** in a carbonyl olefination following modified Takai-Utimoto[66] conditions and subsequent olefin metathesis reaction of the alkene formed resulting in bicycle **560** in 82% yield over two steps (Scheme 103).

Scheme 104. Strategy Towards Gambieric acids by Rainier and Coworkers



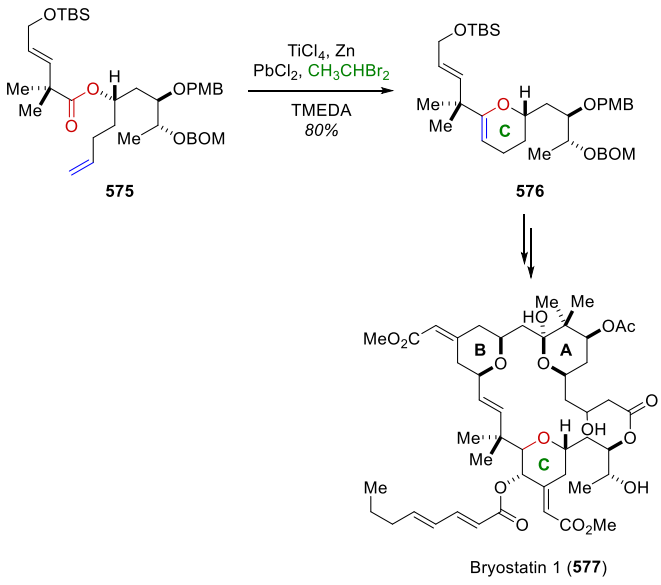
The gambieric acids A-D are also members of the marine ladder toxin family and were isolated from the marine dinoflagellate *Gambierdiscus toxicus* in 1992 by Yasumoto and coworkers.[156] This family of toxins incorporates a common skeletal structure consisting of one 9-membered ring, two 7-membered rings, six 6-membered rings and one 5-membered ring along with 27 stereocenters. The construction of the B-ring of the A-E subunit of gambieric acid was achieved *via* Rainier's previously reported conditions for metal alkylidene-mediated carbonyl-olefin metathesis[65] (Scheme 104). Similar to the previous report, the use of the modified Takai-Utimoto conditions relying on dibromomethane did not result in direct carbonyl-olefin metathesis but rather alkene **563** formed in a carbonyl olefination, which was subsequently subjected to a ruthenium alkylidene catalyst to initiate olefin-olefin metathesis and result in the formation of the desired cyclic enol ether product. Interestingly, when dibromoethane was employed in the reaction protocol to generate the Takai-Utimoto reagent, the cyclic enol ether product **565** corresponding to the direct carbonyl-olefin metathesis product was exclusively formed in 50% yield. Rainier proposed that the carbonyl-olefin metathesis product **565** is formed from an olefin metathesis, carbonyl olefination mechanism suggesting that the more sterically hindered titanium ethylidene preferentially undergoes a reaction with the olefin moiety over the carbonyl in **564**.[156]

Scheme 105. Strategy Towards Brevenal by Rainier and Coworkers



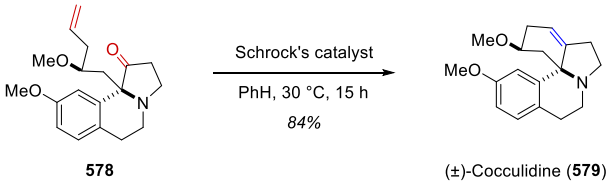
Following their report of the construction of A-E subunits of gambieric acid, Rainier and coworkers reported the total synthesis of brevenal in 2011.[158] Brevenal is also part of the ladder toxin family of natural products and displays a wide variety of biological properties including neurotoxicity and antimicrobial activity.[159] The presence of cyclic ethers allows for the application of Rainier's previously reported olefinic-ester cyclization reaction sequence to enable carbonyl-olefin metathesis.[65] Importantly, the modified Takai-Utimoto reaction conditions developed relying on dibromoethane as reagent allowed for the successful formation of the A (**567**)-, E (**569**)-, C (**571**)- and D (**563**)- ring subunits of brevenal **574** in yields of up to 88% (Scheme 105).

Scheme 106. Strategy Towards Bryostatin 1 by Keck and Coworkers



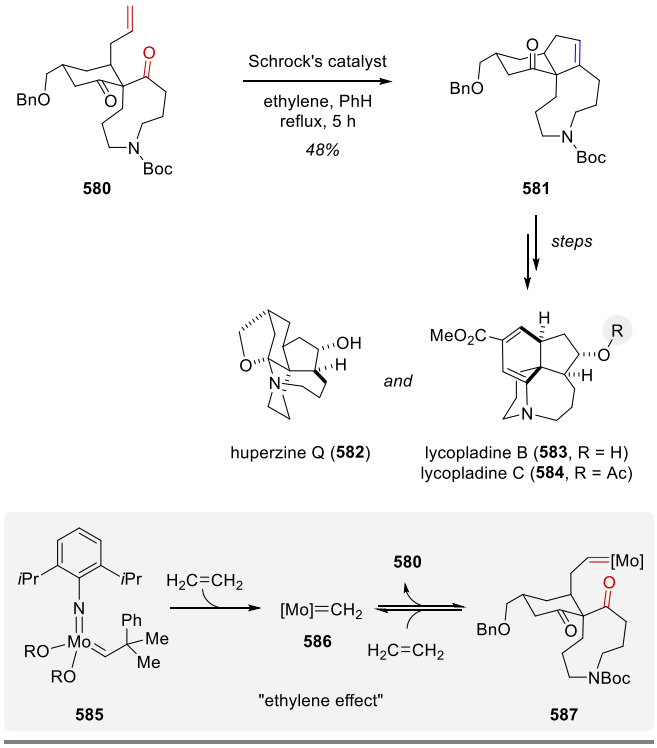
In 2011, Keck and coworkers[160] reported an additional application of carbonyl-olefin metathesis towards the first total synthesis of bryostatin 1, a well-known natural product originally isolated in 1982 by Pettit and coworkers[161] that has shown biological activity against a range of cancers[162] and exhibited activity similar to those of established oncolytic agents such as Taxol.[163] The formation of the C-ring of bryostatin 1 was achieved relying on the modified Takai-Utimoto conditions previously developed by Rainier[157] in 2007 to construct glycal **576** in 80% yield (Scheme 106). This high yielding application allowed for the development of the first total synthesis of bryostatin 1 (**577**) in 30 steps from commercially available (*R*)-isobutyl lactate.

Scheme 107. Synthesis of (±)-Cocculidine by Sarpong and Coworkers



Cocculidine[164] is an *Erythrina* alkaloid with a benz(g)indolizinone scaffold that has been of great interest to the synthetic organic community. Sarpong and coworkers reported the syntheses of (±)-3-demethoxyerythratidinone and (±)-cocculidine **579** in 2013 (Scheme 107).[165] Specifically, completion of the synthesis of (±)-cocculidine (**579**) was achieved in a carbonyl-olefin metathesis reaction mediated by stoichiometric amounts of Schrock's catalyst[166] following reaction conditions originally developed by Grubbs and Fu[60] in 84% yield.

Scheme 108. Synthesis of Huperzine Q, Lycoplanadine B and C by Lei and Coworkers



An additional application of Schrock's metal alkylidene complex for carbonyl-olefin metathesis reactions in natural product synthesis was reported by Lei and coworkers in 2015[167] for the total syntheses of (−)-huperzine Q (**582**) and (+)-lycopladines B (**583**) and C (**584**). The *Lycopodium* alkaloids are a large family of structurally unique natural products with almost 300 isolated members.[168,169] (−)-Huperzine Q (**582**) is a pentacyclic alkaloid that possesses a distinctive aminal moiety and 6 stereogenic centers. The Lei group envisioned a regioselective carbonyl-olefin metathesis reaction of 1,3-diketone **580** to establish the cyclopentene moiety in **581** (Scheme 108). Upon the formation of diketone **580**, the direct metathesis reaction between the olefin and carbonyl moieties was explored and after extensive investigation it was determined that in the presence of a stoichiometric amounts of Schrock's catalyst and ethylene gas (1 atm), carbonyl-olefin metathesis product **581** could be obtained in yields of up to 48%. Control experiments determined that the ethylene gas increased the catalyst's reactivity by converting the initial metal alkylidene **585** into a more active species **586** that underwent a more facile reaction with 1,3-diketone **580.** Furthermore, the ethylene reacted with excess alkylidene **587** regenerating **580** and preventing further byproduct formation.

These examples of using carbonyl-olefin ring-closing metathesis for the synthesis of natural products demonstrate the utility and importance of the overall transformation. Currently, the use of metal alkylidenes remains the state-of-the-art strategy for performing such reactions, leaving room for improvement in both sustainability and catalytic turnover. As the field of carbonyl-olefin metathesis continues to expand, it is expected that the translation of current and future catalytic protocols will be utilized in order to overcome challenges in total synthesis.

9. SUMMARY AND FUTURE PERSPECTIVES

In summary, we have provided a comprehensive overview of the currently available methods for carbonyl-olefin metathesis. These include the Paternò-Büchi cycloadditions followed by the fragmentation of the resulting oxetane, metal alkylidene-mediated strategies, [3+2]-cycloaddition approaches with organocatalysts, Lewis acid-mediated and Lewis acid-catalyzed approaches relying on intermediate oxetanes, and lastly, protocols based on initial carbon-carbon bond formation between carbonyls and alkenes and ensuing Grob-fragmentations. While the earliest studies of carbonyl-olefin metathesis reactions date back to the 1960s, many of

the developments in the field have occurred within the last eight years. These recent efforts have resulted in efficient protocols for catalytic carbonyl-olefin metathesis reactions, including organocatalytic strategies based on strained hydrazines as catalysts, as well as Lewis acid-catalyzed approaches to enable ring-closing, ring-opening, cross and transannular carbonyl-olefin metathesis. Despite the recent accomplishments in reaction development, there remain a number of challenges related to the field of carbonyl-olefin metathesis. The employment of metal alkylidenes currently represents the most applied methods for carbonyl-olefin metathesis in organic synthesis despite the requirement for stoichiometric amounts of the metal alkylidene-complex. Consequently, recent catalytic approaches for carbonyl-olefin metathesis need to be further advanced to broaden the substrate scope with regard to functional group tolerance to ultimately enable efficient applications in complex molecule synthesis. Organocatalytic methods for catalytic carbonyl-olefin metathesis provide a promising alternative but are yet limited in substrate scope. However, especially the ring-opening approaches are desirable as they provide access to products that are complementary to those currently accessible with Lewis acid-catalyzed cross carbonyl-olefin metathesis reactions. The ability to transform a wider variety of cyclic olefin substrates in the existing ring-opening carbonyl-olefin metathesis reaction would allow for a significant expansion in methodology. The use of Lewis acids to catalyze carbonyl-olefin metathesis reactions has shown to have a wide range of applications in terms of the categories of metathesis reaction and substrate scope. Notably, strategies for ring-closing, ring-opening, cross, and transannular carbonyl-olefin metathesis have been developed within the past five years for Lewis acid-catalyzed carbonyl-olefin metathesis. However, the ability to tolerate exceedingly Lewis basic sites and the formation of medium- and larger-sized rings has yet to be attained and represents a current frontier in Lewis acid-catalyzed carbonyl-olefin ring-closing metathesis. Cross carbonyl-olefin metathesis reactions are currently low yielding and remain limited in scope despite invested efforts undertaken by multiple research laboratories. A more robust catalytic cross carbonyl-olefin metathesis strategy will have to comprise more variability in the substitution of the olefin partner, which is currently limited to trisubstituted alkenes, and the reduction of the required excess of aryl carbonyl partner. Future catalyst development will have to focus on an enhanced differentiation between distinct reactivity modes of carbonyl and alkene functionalities. Specifically, while carbonyl-ene reactivity was shown to be crucial in ring-closing carbonyl-olefin metathesis for 6-membered ring systems, it can also provide detrimental byproduct(s) in others, such as ring-opening carbonyl-olefin metathesis. Future, improved reaction protocols will have to overcome these synthetic challenges and hamper unwanted side reactivity to further promote the desired transformation. This is particularly the case for the currently low-yielding Lewis acid-catalyzed ring-opening and cross carbonyl-olefin metathesis reactions. Additional future directions for the field include the application of recently reported carbonyl-olefin metathesis strategies towards efficient polymerization reactions. While initial reports dating back to the 1990s relying on the use of WCl_6 are promising, mechanistic insights into these carbonyl-olefin metathesis polymerizations are limited and future developments in this area will benefit greatly from a better understanding of the controlling features of these transformations.

Acknowledgments

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Author Bios

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Haley Albright received her undergraduate degree from the University of Wisconsin-Madison in 2014 under the supervision of Professor Robert C. West. She then moved to the University of Michigan to pursue her doctoral studies with Professor Corinna S. Schindler where her research focused on the development of a variety of Lewis acid-catalyzed carbonyl-olefin metathesis reaction

methodologies. Upon her graduation in 2019, she joined the department at the University of Michigan as a Lecturer before beginning her independent career at Shepherd University in 2021.

Ashlee J. Davis

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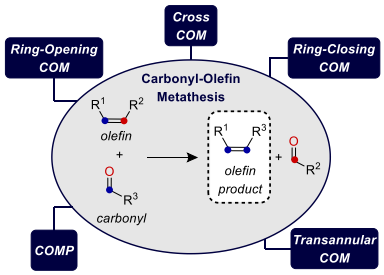
TOC Graphic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