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Mechanistic Investigations of the Iron(III)-Catalyzed Carbonyl-Olefin Metathesis Reaction.

Jacob R. Ludwig¹, Susan Phan², Christopher C. McAtee¹, Paul M. Zimmerman^{*,1}, James J. Devery III^{*,2}, and Corinna S. Schindler^{*,1}

¹University of Michigan, Department of Chemistry, Willard Henry Dow Laboratory, 930 North University Ave., Ann Arbor, MI 48109, US.

²Loyola University Chicago, Department of Chemistry & Biochemistry, Flanner Hall, 1068 West Sheridan Road, Chicago, IL 60660, US.

Abstract

Iron(III)-catalyzed carbonyl-olefin ring-closing metathesis represents a new approach toward the assembly of molecules traditionally generated by olefin-olefin metathesis or olefination. Herein, we report detailed synthetic, spectroscopic, kinetic, and computational studies in order to determine the mechanistic features imparted by iron(III), substrate, and temperature to the catalytic cycle. These data are consistent with an iron(III)-mediated asynchronous, concerted [2+2]-cycloaddition to form an intermediate oxetane as the turnover limiting step. Fragmentation of the oxetane via Lewis acid-activation results in the formation of 5- and 6-membered unsaturated carbocycles.

Graphical Abstract

Introduction

The olefin metathesis reaction is among the most powerful carbon-carbon bond forming reactions known to date and enables the synthesis of complex, unsaturated products from simple alkene precursors in a single transformation.¹ The corresponding carbonyl-olefin metathesis reaction similarly enables the direct construction of carbon-carbon bonds from

*Corresponding Authors corinnas@umich.edu, jdevery@luc.edu, paulzim@umich.edu.

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information.

Experimental data as well as ¹H and ¹³C NMR spectra for all new compounds prepared in the course of these studies are provided in the Supporting Information to this manuscript. The material is available free of charge via the Internet at <http://pubs.acs.org>.

carbonyl and olefin substrates.² However, currently available synthetic strategies of this type have received little iteration and are significantly less advanced as a result. The most prominent approach to carbonyl-olefin metathesis, developed by Grubbs and Fu, relies on stoichiometric amounts of a molybdenum-complex, previously utilized for olefin metathesis (Figure 1A).³ This methodology involves the generation of a substrate alkylidene upon olefin metathesis of a metal alkylidene reagent with an alkene substrate. The resulting alkylidene intermediate can react with a carbonyl to generate oxametallacycle **1** that, upon fragmentation, yields the desired olefin product and an inert metal-oxo complex. Although this reaction is stoichiometric in metal-alkylidene complex, the inherent utility of this approach to carbonyl-olefin metathesis has positioned it as an important tool for carbon-carbon bond formation, most notably in the synthesis of complex, biologically active molecules.⁴ Recently, in an effort to enhance the synthetic utility of carbonyl-olefin metathesis, our group has reported a catalytic variant of this reaction which relies on FeCl₃ as an environmentally benign and economically sustainable catalyst, which was followed by a report from Li and coworkers.⁵ While our previously reported catalytic carbonyl-olefin metathesis strategy has proven useful toward the synthesis of many cyclic scaffolds including cycloalkenes,^{5,6} polycyclic aromatic hydrocarbons,⁷ and azacycles,⁸ we anticipate that a theoretical and experimental investigation of the reaction mechanism can provide insight which will lead to further improvements in the reaction design.

Reaction Development:

Considering the stability of metal-oxo byproducts that result from the traditional metathesis mechanism, we envisioned a distinct design principle for catalytic carbonyl-olefin metathesis which relies on the *in situ* formation of oxetanes **2** as reactive intermediates (Figure 1B). Traditional reactivity between carbonyls and olefins is exemplified by the Prins⁹ and Carbonyl-Ene¹⁰ reactions. These strategies rely on thermal energy or activation of the carbonyl via Brønsted or Lewis acids to garner unsaturated alcohols. In comparison, the direct formation of oxetanes from carbonyls and olefins has been traditionally accomplished via the Paterno-Büchi reaction¹¹ for which initial photochemical excitation of the carbonyl substrate to its triplet state is a prerequisite to oxetane formation. Intriguingly, isolated reports of oxetane formation in the course of Lewis acid-catalyzed Carbonyl-Ene and Prins reactions do exist. Specifically, Kwart and Brechbiel were able to confirm oxetane **5** being formed in the SnCl₄-catalyzed reaction of allylbenzene **3** with diethyl mesoxalate **4**,¹² while Coates and coworkers isolated oxetane **7** in 55% overall yield upon conversion of cyclohexanone **6** with 5 mol% TiCl₄.¹³ These reports of oxetane formation were later rationalized by Singleton and Hang during their mechanistic investigations of Lewis acid-catalyzed Ene reactions based on kinetic isotope effects.¹⁴ Their studies strongly favor a stepwise reaction pathway via intermediate carbocation **11** over a concerted mechanism via transition state **10**. This could explain the isolated reports of oxetane formation upon collapse of the carbocation intermediate. Lewis acid-carbonyl complexes have been studied carefully by a variety of techniques, and charge distribution in the resulting complex is known to significantly vary depending on the Lewis acid.^{15,16,17} Based on these literature reports, we hypothesized that an appropriate Lewis acid could influence the charge distribution in a resulting Lewis acid-carbonyl complex favorably to promote the formation of oxetanes over the corresponding ene-products **12** upon trapping of the respective

carbocation intermediates. Further, we believed that this acid could then facilitate fragmentation to the metathesis product and a carbonyl byproduct.

Results and Discussion

Evaluation of Lewis Acids:

Initial efforts commenced with identifying a suitable substrate to test this design principle for carbonyl-olefin metathesis upon reaction with a variety of Lewis acids.¹⁸ β -Ketoester **13** bearing a pendant isoprenyl moiety was identified as a promising substrate for preliminary investigations based on prior calculations which predicted favorable ring-closing and ring-opening energies of an intermediate oxetane (Figure 3). When aryl ketone **13** was subjected to equimolar amounts of AlCl_3 , the hydrochlorination product **15** was formed exclusively in 66% yield. In comparison, subjection of **13** to identical reaction conditions relying on stoichiometric amounts of the weak Lewis acid, ZnCl_2 , resulted in quantitative reisolation of starting material. However, reaction of aryl ketone **13** with equimolar quantities of SnCl_4 afforded two new products, which were identified as the tertiary alkylation product **17**, formed in 47% yield, and the desired carbonyl-olefin metathesis product **16** in 24% yield. Subsequent experimentation determined FeCl_3 as a Lewis acid particularly capable of promoting the desired carbonyl-olefin metathesis reaction resulting in 50% yield of **16** as the exclusive product of this transformation with complete conversion of starting material. Further studies demonstrated that conducting the reaction with 10 mol% FeCl_3 led to improved overall yields of **16**. Notably, identical catalyst loading of InCl_3 and GaCl_3 also afforded the anticipated metathesis product **16**, albeit in diminished yields of 27% and 55% respectively. Ultimately, 5 mol% of FeCl_3 in dichloroethane at ambient temperature was established as the optimal set of reaction conditions for carbonyl-olefin metathesis. While reagent grade FeCl_3 resulted in the formation of the desired metathesis product in quantitative yields (Table 1, entries 1–3), different sources of sublimed grade FeCl_3 (>99.9%) also afforded quantitative formation of **16** under anhydrous conditions (Table 1, entries 4 and 5). Exposure of **13** with substoichiometric amounts of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ proved equally effective and led to cyclopentene **16** in 96% yield (Table 1, entry 6). In comparison, employing simple Brønsted acids in catalytic or stoichiometric amounts under otherwise identical reaction conditions for carbonyl-olefin metathesis did not result in the desired cyclization products (Table 1, entries 7–10). Specifically, commercially available anhydrous HCl in dioxane as well as experiments generating HCl *in situ* from acetyl chloride and methanol proved ineffective in promoting the desired transformation and afforded no or low conversion of β -ketoester **13**. Further experimentation to evaluate catalytic and equimolar amounts of anhydrous HCl in dichloroethane generated from HCl and CaCl_2 , led to complete recovery of aryl ketone **13**.¹⁹ Together, these results support a mechanism that relies on initial Lewis acid activation of the carbonyl substrate and exclude a Brønsted acid-mediated pathway.

The role of iron(III):

We began our examination of the role that iron(III) plays in the metathesis reaction through observation of concentration effects on the rate of the reaction. Using the reaction defined in Figure 4, we extracted kinetic information by monitoring the concentration of **13** via

reversed-phase ultra performance liquid chromatography coupled with a transmission UV/Vis detector.²¹ All kinetic data were determined from the mean of two different reactions with respect to an internal standard. Intriguingly, lines of constant slope were observed for the concentration of **13** as a function of time, consistent with saturation kinetics. This graphical feature was observed for both 10 and 20 mol% loadings of FeCl₃ with respect to **13**. Comparison of the slopes of decays at these two concentrations of FeCl₃ are consistent first order behavior with respect to FeCl₃.²² These data provide three key insights into the reaction: 1) FeCl₃ is rapidly bound by substrate consistent with interactions between 1,3-dicarbonyls and Fe(III);²³ 2) this binding event occurs prior to the resting state of the catalytic cycle; and 3) the turnover limiting step is impacted by the concentration of FeCl₃.

Having demonstrated that FeCl₃ controls the rate of product formation, it was necessary to investigate how the interaction between Fe(III) and the substrate manifests. Using electron paramagnetic resonance (EPR) spectroscopy, we compared the spectra of complexes **18** and **19** that differ in their unit of unsaturation (Figures 5A and B). Importantly, the EPR studies show no change in oxidation state for iron(III) when FeCl₃ is reacted with substrates **18** and **19** in dichloroethane, following the general protocol developed for carbonyl-olefin metathesis reactions. Additionally, the EPR spectra obtained upon addition of reduced substrate **18** and carbonyl-olefin metathesis substrate **19** to a solution of FeCl₃ in dichloroethane display high degrees of similarity, which suggests binding of FeCl₃ to the carbonyl moiety or both, the carbonyl as well as the ester subunit, according to a Lewis acid activation mechanism.²⁴ Moreover, EPR analysis conducted with **20** under otherwise identical conditions for carbonyl-olefin metathesis suggests that the final product (**16**) has a weaker interaction with FeCl₃ than **13**. Further, the interaction of FeCl₃ with acetone displays an analogous interaction to **19**, providing strong support for the hypothesis that FeCl₃ binds at the carbonyl group of the respective substrates (Figure 5C).

Initial Mechanistic Hypothesis:

Having determined that iron(III) is required to facilitate the turnover-limiting step of the cycle and that the reaction unlikely involves a single electron transfer event, we considered two distinct mechanistic possibilities for oxetane formation, as well as two possibilities for fragmentation of the four-membered ring: 1) a stepwise process involving the formation of carbocation intermediates (**A** and **B**, Figure 6), and 2) concerted [2+2] and retro-[2+2] processes (**C** and **D**, Figure 6). In the stepwise mechanism (**AB**), substrate **13** coordinates FeCl₃, forming complex **19**. The Lewis acid-activation of the carbonyl promotes nucleophilic attack by the pendant olefin to form diastereomeric carbocycles **21** and **21A**. Intermediate **21A** cannot adopt the conformation necessary to form the requisite oxetane **22**. The 1,2-cis geometry of **21** allows for facile cyclization to form **22**. The oxetane intermediate can undergo iron(III)-mediated ring-opening to form tertiary, benzylic carbocation **23**, which upon elimination of acetone (**24**) yields cyclopentene **16**. The lack of alternative species in the product mixture is consistent with reversible carbocycle formation, allowing for interconversion between the diastereomers. Alternatively, a concerted mechanism for oxetane formation and fragmentation (**CD**) would begin with the activated carbonyl of **19** participating in a [2+2]-cycloaddition to form **22** directly. This Lewis acid-

activated species could then undergo a retro-[2+2]-cycloaddition that yields **16** and **24**. It is, also, possible that the mechanism proceeds via mixed process consisting of stepwise-concerted (**AD**) or concerted-stepwise (**CB**) processes (Figure 6).

Identification of the Turnover-limiting Step:

We began the analysis of our mechanistic proposal by an examination of the activation parameters of the turnover-limiting transition state via Eyring analysis. We observed the rate of reaction over temperatures ranging from 35 to 55 °C for **13**, **25**, and **26** (Figure 7).²⁰ These substrates were selected because they are capable of forming tertiary, benzylic, as well as tertiary, benzylic carbocations, respectively. All display zero order behavior with respect to substrate, consistent with saturation kinetics. Further, **13** and **26** display similar rates equal to $(2.29 \pm 0.09) \times 10^{-5} \text{ M s}^{-1}$ and $(2.6 \pm 0.2) \times 10^{-5} \text{ M s}^{-1}$, respectively. Disubstituted alkene **25** displayed a rate of $(1.06 \pm 0.05) \times 10^{-5} \text{ M s}^{-1}$. The Eyring data display high $H^\ddagger$ as well as negative $S^\ddagger$ values, consistent with ordered transition states relative to the resting state of the cycle.²⁵ Importantly, the transition states for oxetane formation and fragmentation will each be more ordered than the substrate-iron complex, requiring further analysis to determine the turnover-limiting step.

To identify whether oxetane formation or fragmentation was turnover-limiting, we sought the value of a secondary kinetic isotope effect (SKIE). This task was accomplished using **26** and the corresponding **26D** as a probe, with deuterium appended β to the carbon of interest (red, Figure 8). If oxetane fragmentation is turnover-limiting, we could observe a normal β -SKIE ($k_H/k_D > 1$, due to hybridization change of sp^3 to sp^2) or no effect. Alternatively if oxetane formation is turnover-limiting, an inverse β -SKIE ($k_H/k_D < 1$, resulting from hybridization change of sp^2 to sp^3) or no effect are the possible results. We observe a faster rate of reaction for **26D** with $k_H/k_D = 0.65 \pm 0.07$, an inverse effect.²⁶ This result is consistent with a change in hybridization of the terminal olefin carbon from sp^2 to sp^3 . This result is consistent with oxetane formation as the turnover-limiting step of the iron(III)-catalyzed carbonyl-olefin metathesis reaction.

Mechanistic Investigations into Oxetane Formation:

In order to identify if oxetane formation follows a stepwise or concerted reaction pathway (Figure 9A), we initiated detailed computational investigations aimed at distinguishing between these two paradigms. The iron(III)-catalyzed carbonyl-olefin metathesis mechanism for ten distinct substrates with varying olefin substitution was investigated using the reaction simulation methodology, ZStruct (Figure 9B).²⁷ This computational technique began with the identification of the reactive atoms of complex **19**. From this starting structure, the program utilized quantum chemistry to perform a systematic search of the combinatorial set of possible reaction coordinates for kinetically and thermodynamically feasible elementary reactions, resulting in approximately 800 possible reaction coordinate combinations (**31**).

The reaction path search resulted in the lowest-barrier pathway leading to oxetane **22** through transition state **32**, a concerted, asynchronous [2+2]-cycloaddition. Intrigued by this result, we began an examination of the electronic mechanism of oxetane formation, because at face value, a concerted [2+2]-cycloaddition is not allowed by orbital symmetry rules, at

least for a synchronous reaction. Figure 10 shows the HOMO of the olefin π system at the onset of coordination to iron(III) (**33**). As the reaction proceeds from **33**, polarization of the HOMO by iron(III) results in a decrease in the distance between the C_a and C_b as well as C_c and O_d (**34**). As the C_a-C_b bond begins to form, the HOMO changes character from π to σ , and delocalizes into the π system of the aryl group (**35**). This delocalization occurs because the new C_a-C_b σ bond is aligned to interact with the aryl π system, assisting the transformation. The overall orbital change from substrate to oxetane formation results in a partial positive charge at C_c (**36**) prior to immediate ring closure by the C_c-O_d bond (**37**). Orbital symmetry is conserved along this single-step, asynchronous reaction coordinate. The electronically smooth transformation therefore occurs without unphysical breaking of the orbital symmetry, consistent with the Woodward-Hoffmann rules.

How could a pathway that nominally requires an ionic intermediate be concerted? Examination of the potential energy surface (PES) of the cycloaddition event provides further insight into the nature of the reaction path (Figure 11). A stepwise reaction with an ionic intermediate (orange dash) is contrasted to a concerted asynchronous reaction shown as a blue, solid line. Here, both reaction profiles are highly similar in that the rate-limiting barrier is the same. Further, the carbocationic structure in the middle of the reaction coordinate is not particularly stable. The concerted process thus undergoes two electronic character changes in a single elementary step, but since these changes occur asynchronously, the reaction conserves overall orbital symmetry.

In comparison to these computational results, our initial investigations of the substrate scope of the iron(III)-catalyzed carbonyl-olefin metathesis had shown that isoprenyl-derived alkenes, such as **13**, proved superior and resulted in quantitative formation of the desired metathesis products. These results first led us to favor a stepwise pathway for the carbonyl-olefin metathesis reaction, later also favored by Li and coworkers.^{5c} In order to clarify the nature of oxetane formation, we employed trapping experiments with equimolar amounts of various nucleophiles in an attempt to trap the possible carbocationic intermediates as the corresponding esters, ethers, or amides (Table 2, entries 2–7). No products that result from the intermolecular addition of a nucleophile to a cation were detected. However, we did observe lower yields of the desired metathesis products with stoichiometric methanol, isopropanol, or acetonitrile. As a result of this diminished reactivity, the remaining material recovered was unreacted **13** (Table 2, entries 4, 5, 7).

We then expanded our search of possible carbocation intermediates via substrates with differing olefin substitution patterns (**25–26**, **38–43**, Table 3). Enthalpic barriers for the formation of oxetanes resulting from olefins **13**, **25–26**, and **38–43** range from 13.9 kcal mol⁻¹ for **13** to 31.4 kcal mol⁻¹ of terminal alkene **43** (Table 3). Importantly, the values of $H^\ddagger$ for **13**, **25**, and **26** are in agreement with those measured by Eyring analysis (Figure 7). Substrate **43** was found to have particularly high barriers due to the lack of substitution at the olefin, which cannot stabilize charge build-up occurring in the oxetane forming transition state. Carbonyl-olefin metathesis of **43** is, therefore, kinetically prohibitive due to the ring closure step. For substrates **13**, **25–26**, and **38–41**, the activation barriers are low enough for oxetane formation to proceed. This reaction pathway for oxetane formation identified using ZStruct was found to explain reactivity and inactivity of the metathesis precursors

investigated (**13**, **25-26**, and **38-43**, Table 3). Substrates with barriers significantly over approximately 20 kcal mol⁻¹ result in no formation of the desired metathesis products while intermediate activation enthalpies result in mediocre yields of the corresponding products. In all cases starting from the FeCl₃-bound substrate **27**, examination of the PES of each substrate predicts an analogous reaction coordinate to that displayed in Figure 11: concerted, asynchronous pathways with unstable carbocationic intermediates.

Taken together, the EPR, kinetic, theoretical, and synthetic studies yield the following results: 1) Success of metathesis is related to the Lewis acidity of the metal catalyst, with maximum yield observed via iron(III). 2) The metathesis process occurs efficiently regardless of FeCl₃ source or hydration of the metal center. 3) HCl, which could be formed via hydrolysis of FeCl₃, does not catalyze the reaction. 4) FeCl₃ binds at the carbonyl(s) of the substrate without an electron transfer event. 5) The turnover-limiting transition state of the cycle is ordered and displays high levels of bond reorganization energy. 6) The reaction displays an inverse β -SKIE, consistent with oxetane formation as the turnover-limiting step. 7) The π system of the aryl group facilitates delocalization of the HOMO, conserving orbital symmetry. 8) The potential energy surface of oxetane formation displays negligible difference in transition state barriers between stepwise and concerted, asynchronous oxetane formation. 9) Intermolecular nucleophilic trapping experiments are consistent with no persistent carbocation intermediate. These observations leave one point requiring clarification: Does oxetane formation proceed via a stepwise process featuring an ionic intermediate or via a concerted asynchronous [2+2] cycloaddition?

The reaction coordinate of the stepwise process displays a higher barrier for initial addition of the olefin to the activated carbonyl, resulting in the formation of an iron-stabilized oxygen anion and a carbocation (Figure 11). Subsequent formation of the four-membered ring then proceeds via a lower barrier. Importantly, this process requires that formation of the ionic intermediate proceeds without a change in hybridization of the terminal carbon in the pendant olefin (Figure 11) in the turnover-limiting step. If, alternatively, the ring formation were accomplished via a concerted, asynchronous cycloaddition, the hybridization of the terminal carbon in the pendant olefin would change from sp² in the olefin to sp³ in the oxetane, consistent with an inverse β -SKIE. When all the theoretical and empirical data are considered together, they are consistent with concerted, asynchronous formation of the oxetane intermediate as the turnover-limiting step of the catalytic cycle.

Mechanistic Investigations into Oxetane Fragmentation:

We subsequently investigated the fragmentation of oxetane **30**, which could also proceed via a concerted or stepwise pathway (Figure 12). Specifically, oxetane **30** can undergo concerted fragmentation to the metathesis product **46** or proceed in a stepwise mechanism via carbocation **45** upon heterolysis of the carbon-oxygen bond. Invoking our previous mechanistic probes **13**, **25-26**, and **38-43**, which vary in their olefin subunit, we sought to interrogate their respective ring-opening events computationally (Tables 4 and 5).

Both mechanistic scenarios of oxetane fragmentation were explored separately in our theoretical investigations. Oxetane ring-opening was found to proceed in three conceptually distinct steps based on these theoretical investigations (Tables 4 and 5). The first is rotation

of the phenyl ring adjacent to the original carbonyl moiety to make it coplanar with the olefin which will subsequently form. This elementary step aligns the π system to facilitate ring-opening, and displays negligible barriers of rotation (less than 3 kcal mol⁻¹) across the range of substrates investigated (**13**, **25-26**, and **38-43**).

Subsequent to the alignment step, the C–O as well as C–C bonds must break, either in a concerted fashion (**44**) or stepwise pathway by first breaking the C–O bond to form carbocation **45** (Figure 12). This process was found to occur in a substrate-dependant fashion. Substrate **13** with dimethyl substitution on the olefin does not have stationary points on the potential energy surface corresponding to an ionic intermediate **45**. Conversely, substrates **25-26** and **38-43** were found to have ionic structures of modest stability, corresponding to plateaus on their respective energy surfaces. The energies for these structures are found to be relatively high, allowing low barriers for elimination to **46** and **47**. These barriers indicate that the ionic structure will be extremely short-lived.

To provide corroboration of the simulation results obtained in the oxetane fragmentation, we designed mechanistic probe molecules **51–54**. All structures bear a pendant alcohol with the potential to trap an intermediate benzylic carbocation, but differ in their olefin substitution (Table 6). Isoprenyl-derived alcohol **51** resulted in the formation of the corresponding metathesis product **49** in high yields of 87% at 100% conversion. Importantly, we were not able to isolate and characterize any other compounds from the reaction mixture. However, styrenyl-derived primary alcohols **52-54** resulted in much lower yields of the desired metathesis product **49** while high conversions of the respective starting materials were observed. Although no potential carbocation trapping products were isolated in the course of the reactions of **52-54**, a complex mixture of products was formed in these reactions in addition to the desired metathesis product. In comparison to the results obtained with isoprenyl-derived substrate **51**, forming the metathesis product **49** in high yields, the lower yields observed with styrenyl-derivatives **52-54** can be rationalized based on decomposition pathways resulting from an intermediate benzylic carbocation. These data suggest that an intramolecular process may occur at a sufficient rate to interact with the charged intermediate.

Final mechanistic proposal:

Collectively, our data are consistent with two olefin-dependent mechanisms of iron(III)-catalyzed carbonyl-olefin metathesis (Figures 13 and 14). For substrates bearing a prenyl substitution pattern (**13**), a concerted-concerted mechanism (**CD** in Figure 6) operates, beginning with coordination to iron(III) to form **19**, a Lewis acid-mediated concerted, asynchronous [2+2]-cycloaddition (**32**) forms oxetane **22**. The four-membered ring then undergoes an iron(III)-mediated concerted, asynchronous retro-[2+2]-cycloaddition (**55**) to form the cycloalkene product and the carbonyl byproduct, as well as turn over the catalyst. Alternatively, when a styrenyl derivative participates in the reaction, complex **57** forms oxetane **59** via a concerted, asynchronous [2+2]-cycloaddition (**58**), which then undergoes heterolysis (**60**) to form **61** (Figure 14). This charged intermediate **61** eliminates benzaldehyde **63** to form metathesis product **16**.

Conclusion

The mechanism of iron(III)-catalyzed carbonyl-olefin ring-closing metathesis was investigated based on computational, kinetic, and synthetic experiments. The combination of theory and experiment has not only given us insight into the mechanistic properties of this reaction system, but has allowed us to propose two catalytic cycles that are dependent upon substitution of the olefin. Iron(III)-chloride acts exclusively as a Lewis acid, activating the carbonyl-oxygen of the substrate as the resting state of the cycle. Upon activation, all substrates initially undergo turnover-limiting oxetane formation in a concerted, asynchronous reaction mechanism. For substrates bearing a prenyl-substitution, oxetane fragmentation similarly proceeds via a concerted, asynchronous reaction mechanism in the product-forming step. However, substrates bearing a styrenyl substitution pattern fragment via an intermediate carbocation followed by elimination to the products. It is important to note that our current hypothesis is reliant upon the collective insight gained from corroboration of computational, kinetic, and synthetic analyses. In the absence of one or two of these methods, we would have arrived at a different proposal. We are currently examining the mechanism of other iron(III)-catalyzed carbonyl-olefin ring-closing metathesis systems to determine the prevalence of the concerted, asynchronous [2+2]-cycloaddition. The results of these studies will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A Carbonyl-Olefin Metathesis (stoichiometric in metal): **B Carbonyl-Olefin Metathesis (Lewis acid (LA)-catalyzed):** **C Reactivity between carbonyls and olefins:***Prins Reaction:* *Carbonyl-Ene Reaction:* *Paterno-Büchi:* **Figure 1.**

Design principles for carbonyl-olefin metathesis reactions (A and B). Reactions of carbonyls and olefins (C).

A Formation of Oxetanes in Carbonyl-Ene and Prins Reactions

H. Kwart and M. Brechbiel (1982)

R.B. Miles, C.E. Davis, R.M. Coates (2006)

B Mechanistic Investigations of Lewis acid-catalyzed Ene Reactions

D.A. Singleton and C. Hang (2000)

Figure 2.
Mechanistic investigations of carbonyl-ene reactions.

Figure 3. Evaluation of Lewis acids in the carbonyl-olefin ring-closing metathesis reaction of β -ketoester **13**. *Reactions are run under catalytic conditions with 10 mol% Lewis acid in dichloroethane as solvent.

Figure 4.
Rate order determination in the formation of cyclopentene **16**.²⁰

Figure 5.
EPR-experiments in the Lewis acid-catalyzed carbonyl-olefin metathesis reaction.

Figure 6.

Mechanistic hypotheses for the iron(III)-catalyzed carbonyl-olefin metathesis reaction that proceed via oxetane **22**: 1) stepwise oxetane formation via **21** (**A**), followed by stepwise fragmentation via **23** (**B**); 2) concerted oxetane formation (**C**), followed by concerted fragmentation (**D**); 3) stepwise oxetane formation via **21** (**A**), followed by concerted fragmentation (**D**); 4) concerted oxetane formation (**C**), followed by stepwise fragmentation via **23** (**B**).

Eyring analysis:

$$\Delta H_{\text{calc}}^{\ddagger} = 13.9 \text{ kcal mol}^{-1}$$

$$\Delta H_{\text{exp}}^{\ddagger} = 14 \pm 1 \text{ kcal mol}^{-1}$$

$$\Delta S^{\ddagger} = -34 \pm 5 \text{ cal mol}^{-1} \text{ K}^{-1}$$

$$\Delta H_{\text{calc}}^{\ddagger} = 15.1 \text{ kcal mol}^{-1}$$

$$\Delta H_{\text{exp}}^{\ddagger} = 16 \pm 1 \text{ kcal mol}^{-1}$$

$$\Delta S^{\ddagger} = -29 \pm 4 \text{ cal mol}^{-1} \text{ K}^{-1}$$

$$\Delta H_{\text{calc}}^{\ddagger} = 14.2 \text{ kcal mol}^{-1}$$

$$\Delta H_{\text{exp}}^{\ddagger} = 15.5 \pm 0.7 \text{ kcal mol}^{-1}$$

$$\Delta S^{\ddagger} = -30 \pm 2 \text{ cal mol}^{-1} \text{ K}^{-1}$$

Figure 7.

Investigation of activation parameters of the iron(III)-catalyzed carbonyl-olefin metathesis reaction.²⁰

Kinetic Isotope Effect Studies

Figure 8.
 Secondary β -kinetic isotope effect studies of the carbonyl-olefin metathesis reaction.¹⁹

A Concerted vs. Stepwise Formation of Oxetane 30

B ZStruct Method Description

Figure 9.
ZStruct reaction simulation methodology.

Fe-Substrate Complex:

Figure 10.
HOMO of β -ketoester substrate during oxetane formation.

Figure 11.

Figurative potential energy surfaces (PES) showing the difference between concerted asynchronous and stepwise reaction pathways that are electronically similar.

Figure 12.
Concerted versus stepwise fragmentation of oxetanes.

Figure 13. Complete reaction pathway for isoprenyl-derived substrates in the iron(III)-catalyzed carbonyl-olefin metathesis reaction.

Figure 14.
Complete reaction pathway for styrenyl-derived substrates in the iron(III)-catalyzed carbonyl-olefin metathesis reaction.

Table 1. Effect of different sources of FeCl₃ and HCl on the carbonyl-olefin metathesis reaction.

entry	acid	mol(%)	yield 16 (%)	conversion (%)
1	FeCl ₃ (97%) ^a	10	99	100
2	FeCl ₃ (97%) ^a	10	99	100
3	FeCl ₃ (anhydrous, 98%) ^b	10	99	100
4	FeCl ₃ (>99.9%) ^c	10	99	100
5	FeCl ₃ (anhydrous, >99.9%) ^d	10	96	100
6	FeCl ₃ ·6H ₂ O (>99%) ^e	10	96	100
7	HCl (in anhydrous dioxane) ^f	10	0	0
8	HCl (generated <i>in situ</i> from AcCl and MeOH)	20	0	10
9	HCl (in anhydrous DCE) ^g	5	0	0
10	HCl (in anhydrous DCE) ^g	100	0	0

Conditions: ketone (1.0 equiv), acid (5–100 mol%) in anh. DCE (0.01 M), 24 h^{a)} Sigma Aldrich, reagent grade (97%)^{b)} Strem, anhydrous (98%)^{c)} Sigma Aldrich, sublimed grade, >99.9% trace metal basis^{d)} Sigma Aldrich, anhydrous, >99.9% trace metal basis^{e)} Sigma Aldrich, puriss, 99%^{f)} commercial reagent HCl (4 M in anh. Dioxane)^{g)} HCl in anh. DCE generated from concentrated HCl and CaCl₂.

Table 2.

Nucleophilic trapping experiments of the iron(III)-catalyzed carbonyl-olefin metathesis reaction.

entry	nucleophile	yield 16 (%)	conversion (%)
1	-	99	100
2	benzoic acid (BzOH)	94	100
3	acetic acid (AcOH)	98	100
4	methanol (MeOH)	54	56
5	isopropanol (<i>i</i> PrOH)	46	54
6	nitromethane 9 (MeNO ₂)	99	100
7	acetonitrile (MeCN)	18	20

Conditions: All reactions were performed using 0.18 mmol β-ketoster, 0.009 mmol FeCl₃ in DCE (0.01 M) at rt for 24 h.

Table 3.

Theoretical investigations of oxetane formation.

entry	substrate	yield (%)	28	30
1		13	99	13.9 -0.6
2		38	70	14.3 5.1
3		25	60	15.1 4.8
4		39	49	17.1 3.2
5		40	62	13.5 9.3
6		26	49	14.2 8.7
7		41	60	18.2 11.0
8		42	0	20.6 -2.4
9		43	0	31.4 -1.4

^aConditions: Ketone (1.0 equiv), FeCl₃ (5 mol%) in DCE (0.01 M), 1–12 h.

Table 4.

Theoretical investigations of concerted oxetane fragmentation.

entry	substrate	yield (%)	44	46
1		13	99	14.2 -1.1
2		38	70	16.0 3.6
3		25	60	15.7 3.7
4		39	49	11.0 1.3
5		40	62	16.1 3.1
6		26	49	16.5 -0.9
7		41	60	17.3 4.9
8		42	0	7.7 1.7
9		43	0	7.6 7

^aConditions: Ketone (1.0 equiv), FeCl₃ (5 mol%) in DCE (0.01 M), 1–12 h.

Table 5.

Theoretical investigations of stepwise oxetane fragmentation.

Reaction scheme showing the stepwise fragmentation of an oxetane (36) to a ketone (47) via intermediates 45 and 46. The scheme includes transition state energy values (E_u in kcal mol⁻¹) for each step.

entry	substrate	yield (%)	ring-opening	
1		13	99	n.a
2		38	70	2.2
3		25	60	1.8
4		39	49	2.6
5		40	62	1.8
6		26	49	1.0
7		41	60	3.7
8		42	0	3.3
9		43	0	3.0

^a **Conditions:** Ketone (1.0 equiv), FeCl₃ (5 mol %) in DCE (0.01 M), 1–12 h.

Table 6.

Intramolecular trapping experiments of benzylic carbocations.

entry	substrate	yield (%)	conversion (%)
1		51	87
2		52^a	35
4		53	16
6		54^b	29

Conditions: Ketone (1.0 equiv), FeCl₃ (5 mol %) in DCE (0.01 M), 1–12 h^a) 80 °C for 12 h^b) room temperature for 48 h