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

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MECHANISTIC INVESTIGATIONS OF THE IRON(III)-CATALYZED CARBONYL-OLEFIN METATHESIS REACTION

A THESIS SUBMITTED TO
THE FACULTY OF THE GRADUATE SCHOOL
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MASTER OF SCIENCE

PROGRAM IN CHEMISTRY & BIOCHEMISTRY

BY
SUSAN PHAN
CHICAGO, IL
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ACKNOWLEDGEMENTS

Throughout my time at LUC, I had struggled with and overcome a number of challenges—internal, external, academic, and non-academic. I would like to thank those who have provided me with stability, support, advice, and friendship.

Prof. James J. Devery, III once shared a story of his pursuit for emotional stability while in graduate school; the down-and-out feeling I had gleaned was reminiscent of my own. Since then, I have clung to his advice of finding stability where I could—in my work, elbow-deep. He, of course, has provided much beyond this. He has consistently been there to advise and mentor, provide support of any kind, and act as a guiding light through much darkness. His ambitious and persistent nature, high standards, and lightheartedness are inspirational, which I wish to carry forward with me every day.

Next, I would like to thank my close colleague and friend, Carly S. Hanson. Working in the same lab, she has always been there through the darkest and brightest of times, and of course, everything in between. Her friendship will always be treasured.

Finally, I would like to thank my dad, Thao Phan; my stepmom, Thao Nguyen; my closest cousin, Nhung Nguyen; and my best friend, Elise Crary for their endless love and support.
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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 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 five- and six-membered unsaturated carbocycles.
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 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.

Figure 1. Design principles for carbonyl-olefin metathesis reactions (A and B). Reactions of carbonyls and olefins (C).
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. 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, that was followed by a report from Li and coworkers. While our previously reported catalytic carbonyl-olefin metathesis strategy has proven useful toward the synthesis of many cyclic scaffolds including cycloalkenes, polycyclic aromatic hydrocarbons, and azacycles, 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 Prins and carbonyl-ene 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 reaction 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 carboyl-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, while Coates and coworkers isolated oxetane 7 in 55% overall yield upon conversion of cyclohexanone 6 with 5 mol% TiCl₄. 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. 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.\textsuperscript{15,16,17} On the basis of 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 \textbf{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.\textsuperscript{18} \(\beta\) -Ketoester \textbf{13} bearing a pendant isoprenyl moiety was identified as a promising substrate for preliminary investigations on the basis of prior calculations, which predicted favorable ring-closing and ring-opening energies of an intermediate oxetane (Figure 3). When aryl ketone \textbf{13} was subjected to equimolar

![Figure 3](image-url)
amounts of AlCl₃, 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, ZnCl₂, resulted in quantitative reisolation of starting material. However, reaction of aryl ketone 13 with equimolar quantities of SnCl₄ 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 FeCl₃ 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% FeCl₃ led to improved overall yields of 16.

Notably, identical catalyst loading of InCl₃ and GaCl₃ also afforded the anticipated metathesis product 16, albeit in diminished yields of 27% and 55% respectively. Ultimately, 5 mol% of FeCl₃ in dichloroethane at ambient temperature was established as the optimal set of reaction conditions for carbonyl-olefin

Table 1. Effect of Different Sources of FeCl₃ and HCl on the Carbonyl-Olefin Metathesis Reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>mol (%)</th>
<th>yield 16 (%)</th>
<th>conversion (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>FeCl₃ (97%)</td>
<td>10</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>FeCl₃ (97%)</td>
<td>10</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>FeCl₃ (anhdyrous, 98%)</td>
<td>10</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>FeCl₃ (&gt;99.9%)</td>
<td>10</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>FeCl₃ (anhdyrous, &gt;99.9%)</td>
<td>10</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>FeCl₃·6H₂O (&gt;99%)</td>
<td>10</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>HCl (in anhydrous dioxane)</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>HCl (generated in situ from AcCl and MeOH)</td>
<td>20</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>HCl (in anhydrous DCE)</td>
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<td>10</td>
<td>HCl (in anhydrous DCE)</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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.
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 FeCl$_3$·6H$_2$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.

**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. 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); (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 metathesis substrate 13 and its reduced analogue, following the general protocol developed for carbonyl-olefin metathesis reactions. Additionally, the EPR spectra of complexes 18 and 19 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. 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 does 13. Further, the interaction of FeCl₃ with acetone displays an
analogous interaction to that of 19, providing strong support for the hypothesis that FeCl$_3$ 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). 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 $(2.29 \pm 0.09) \times 10^{-5}$ and $(2.6 \pm 0.2) \times 10^{-5}$ M s$^{-1}$, respectively. Disubstituted alkene 25 displayed a rate of $(1.06 \pm 0.05) \times 10^{-5}$ M s$^{-1}$. The Eyring data display high $\Delta H^\ddagger$ as well as negative $\Delta S^\ddagger$ values, consistent with ordered transition states relative to the resting state of the cycle. 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 $\beta$ to the carbon of interest (red, Figure 8). If oxetane fragmentation is turnover-limiting, we could observe a normal $\beta$-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 $\beta$-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. 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.** 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 10 distinct substrates with varying olefin substitution was investigated using the reaction simulation methodology, ZStruct (Figure 9B). 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\textsubscript{c} (36) prior to immediate ring closure by the C\textsubscript{c}—O\textsubscript{d} bond (37). Orbital symmetry is conserved along this single-step, asynchronous reaction coordinate\textsuperscript{28}. 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

<table>
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<th>bond lengths:</th>
<th>reaction coordinate</th>
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<td>C\textsubscript{c}—C\textsubscript{c}</td>
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<tr>
<td>C\textsubscript{c}—O\textsubscript{d}</td>
<td>3.11Å</td>
</tr>
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</table>

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.
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.\textsuperscript{5c} 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 \(\Delta H^\ddagger\) 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 FeCl\(_3\)-bound substrate 27, examination of the PES of each substrate predicts a reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>yield (%)</th>
<th>28</th>
<th>30</th>
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<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>13</td>
<td>99</td>
<td>13.9</td>
</tr>
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<td>2</td>
<td>38</td>
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</tr>
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<td>9</td>
<td>H</td>
<td>43</td>
<td>0</td>
<td>31.4</td>
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\(^{a}\)Conditions: Ketone (1.0 equiv), FeCl\(_3\) (5 mol\%) in DCE (0.01 M), 1-12 h.
coordinate analogous 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 FeCl$_3$ source or hydration of the metal center. (3) HCl, which could be formed via hydrolysis of FeCl$_3$, does not catalyze the reaction. (4) FeCl$_3$ 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 $\beta$-SKIE, consistent with oxetane formation as the turnover-limiting step. (7) The $\pi$ 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 sp$^2$ in the olefin to sp$^3$ in the oxetane, consistent with an inverse $\beta$-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 that will subsequently form. This elementary step aligns the $\pi$ 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 in a stepwise pathway by first breaking the C–O bond to form carbocation 45 (Figure 12). This process was found to occur in a substrate-dependent 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.

### Table 4. Theoretical Investigations of Concerted Oxetane Fragmentation

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>yield (%)</th>
<th>44</th>
<th>46</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>13</td>
<td>99</td>
<td>14.2</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>38</td>
<td>70</td>
<td>16.0</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>25</td>
<td>60</td>
<td>15.7</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>39</td>
<td>49</td>
<td>11.0</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>40</td>
<td>62</td>
<td>16.1</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>26</td>
<td>49</td>
<td>16.5</td>
</tr>
<tr>
<td>7</td>
<td>Cl</td>
<td>41</td>
<td>60</td>
<td>17.3</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>42</td>
<td>0</td>
<td>7.7</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>43</td>
<td>0</td>
<td>7.6</td>
</tr>
</tbody>
</table>
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.

Table 5. Theoretical Investigations of Stepwise Oxetane Fragmentation.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>yield (%)</th>
<th>ring-opening</th>
<th>(E_a) (kcal mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>13</td>
<td>99</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>70</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>25</td>
<td>60</td>
<td>1.8</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>39</td>
<td>49</td>
<td>2.6</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
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<td></td>
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<tr>
<td>6</td>
<td>Ph</td>
<td>26</td>
<td>49</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>Cl</td>
<td>41</td>
<td>60</td>
<td>3.7</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>42</td>
<td>0</td>
<td>3.3</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>43</td>
<td>0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 6. Intramolecular Trapping Experiments of Benzylic Carbocations.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>yield (%)</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>51</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>52(^a)</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>53</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>54(^b)</td>
<td>29</td>
<td>86</td>
</tr>
</tbody>
</table>
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 on the basis of 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.
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.
Conclusion

The mechanism of iron(III)-catalyzed carbonyl-olefin ring-closing metathesis was investigated on the basis of 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.
REFERENCE LIST


(5)  a) This work was first reported as Ludwig, J.R.; Gianino, J.B.; Schindler, C.; Abstracts of Papers, 250th ACS National Meeting & Exposition, Boston, MA, United States, August 16th-20th, 2015, ORGN-388; b) Ludwig, J.R.; Zimmerman, P.M.; Gianino, J.B.; Schindler, C.S. Nature 2016, 533, 374. c) Ma, L.; Li, W.; Xi, H.; Bai, X.; Ma, E.; Yan, X.; Li, Z. Angew. Chem. Int. Ed. 2016, 55, 10410.


(20) See the Supporting Information for more details.


(25) For an example of analogous activation parameters for a [2+2]-cycloaddition that forms a [3.2.0] system, see: Alvarez, P.; Lastra, E.; Gimeno, J.; Bassetti, M.; Falvello, L. R. J. Am. Chem. Soc. 2003, 125, 2386.


VITA

Phan graduated from the University of Iowa with a bachelor of science degree in biochemistry in 2015. During her undergraduate career, she performed retroviral cloning in the Taylor lab and organic synthesis of an oral antimicrobial agent in the Nguyen lab. As a graduate student of the Devery group at Loyola University Chicago, Phan developed mechanistic profiles of two Lewis acid-catalyzed reactions via kinetic experiments: (1) Fe(III)-activated carbonyl-olefin ring-closing metathesis and (2) Zn(II)/TMSCl-catalyzed hydroarylation. These studies were performed via ultra-performance liquid chromatography (UPLC), real-time in situ Fourier-transform infrared spectroscopy (ReactIR), and $^{13}$C nuclear magnetic resonance. Upon gaining experience in a range of common tools, instrumentation, and techniques in organic chemistry, as well as knowledge in the field, Phan realized a strong interest in organometallic bond activation and is currently interested in pursuing method development of inert C-C bond functionalization.