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# Lewis Acid Catalyzed Carbonyl–Olefin Metathesis

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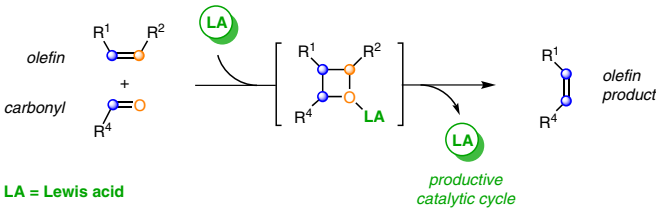


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**Abstract** Olefin–olefin metathesis has led to important advances in diverse fields of research, including synthetic chemistry, materials science, and chemical biology. The corresponding carbonyl–olefin metathesis also enables direct carbon–carbon bond formation from readily available precursors, however, currently available synthetic procedures are significantly less advanced. This Synpacts article provides an overview of recent achievements in the field of Lewis acid mediated and Lewis acid catalyzed carbonyl–olefin metathesis reactions.



**Key words** carbonyl–olefin metathesis, Lewis acid, iron, base metal

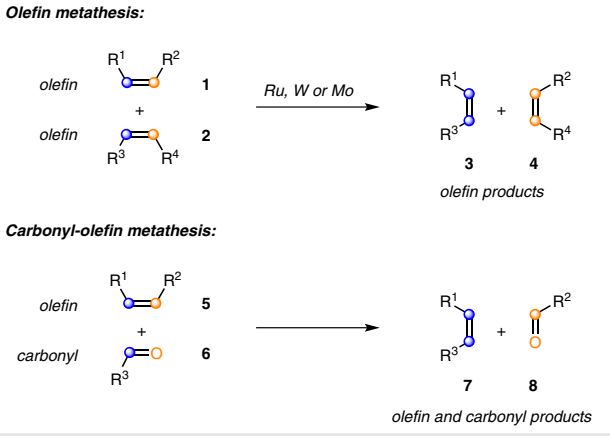
**Jacob R. Ludwig** grew up in Lake Orion Michigan and received his BSc in chemistry from Michigan State University in 2014 where he performed organic chemistry research in the laboratory of Prof. Jetze J. Tepe. After graduation, he joined the Schindler lab at the University of Michigan to pursue his PhD degree in organic chemistry.
**Corinna S. Schindler** grew up in Schwäbisch Hall, Germany and received her diploma in chemistry from the Technical University of Munich. After a research stay with Prof. K. C. Nicolaou at the Scripps Research Institute in La Jolla, CA, she joined the group of Prof. Erick M. Carreira at the ETH Zürich, Switzerland for her graduate studies. She then returned to the US to conduct postdoctoral studies with Prof. Eric N. Jacobsen at Harvard University before starting her independent career at the University of Michigan in 2013.

The formation of carbon–carbon bonds is of fundamental importance in the field of synthetic organic chemistry and is therefore 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 **1** and **2** (Scheme 1) to result in the formation of two distinct olefinic products **3** and **4** is among the most powerful catalytic carbon–carbon bond-forming reactions known and has led to profound synthetic developments in the petroleum, materials, agricultural, and pharmaceutical industries.[1] The corresponding carbonyl–olefin metathesis reaction between an olefin **5** and a carbonyl **6** (Scheme 1) similarly enables the direct construction of carbon–carbon bonds, resulting in the formation of olefin **7** and carbonyl **8**,[2–4] and has the potential to have an analogous impact on synthetic strategy (Scheme 1).[5] However, compared to the olefin–olefin metathesis reaction, currently available procedures for carbonyl–olefin metathesis are significantly less advanced. This Synpacts article is focused on our work in the area of Lewis acid mediated and Lewis acid catalyzed carbonyl–olefin metathesis reactions.[6]

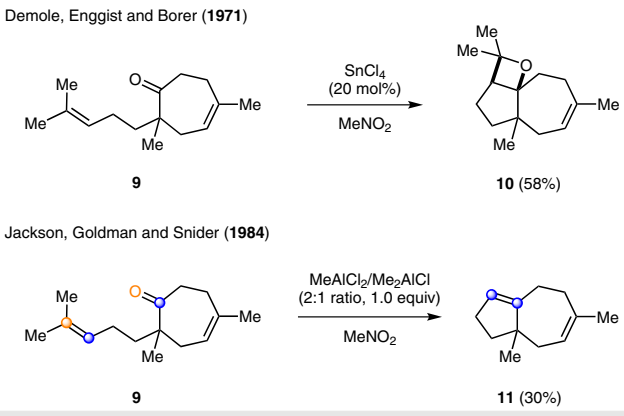
## 1 Lewis Acid Mediated Carbonyl–Olefin Metathesis

In their studies towards the synthesis of carotol sesquiterpenes, Demole, Enggist, and Borer reported the exclusive



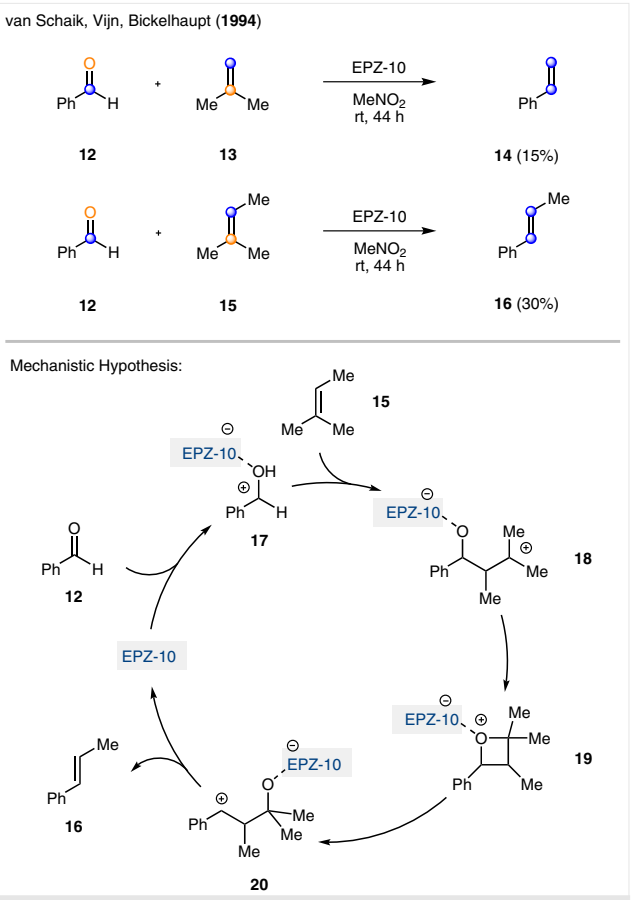

**Scheme 1** Olefin–olefin metathesis vs. carbonyl–olefin metathesis

formation of oxetane **10** in 58% yield upon treatment of cycloheptanone **9** with 20 mol% $SnCl_4$.[7] The authors propose a stepwise mechanistic pathway relying on an intramolecular [2+2] cycloaddition to form the corresponding *cis*-oxetane **10** as the sole product (Scheme 2). In 1984, Snider and coworkers revisited the original reports by Demole in the course of their studies of intramolecular ene reactions.[8] When cycloheptanone **9** was treated with stoichiometric amounts of $MeAlCl_2$/$Me_2AlCl$ (in a 2:1 ratio) in dichloromethane for ten hours, the formation of diene **11** was observed in 30% yield. Snider and coworkers describe **11** as the product of a metathesis reaction which they presume to proceed via a stepwise cycloaddition to form intermediate oxetane **10** and a subsequent retrocycloaddition to result in **11** along with the loss of acetone (Scheme 2). Notably, the authors report that no reaction occurred upon treatment of **9** with $Me_{1.5}AlCl_{1.5}$, however, a complex mixture resulted when cycloheptanone **9** was subjected to stoichiometric amounts of $MeAlCl_2$, indicating the importance of Lewis acid strength in mediating the carbonyl–olefin metathesis reaction.




**Scheme 2** First example of a Lewis acid mediated carbony–olefin metathesis

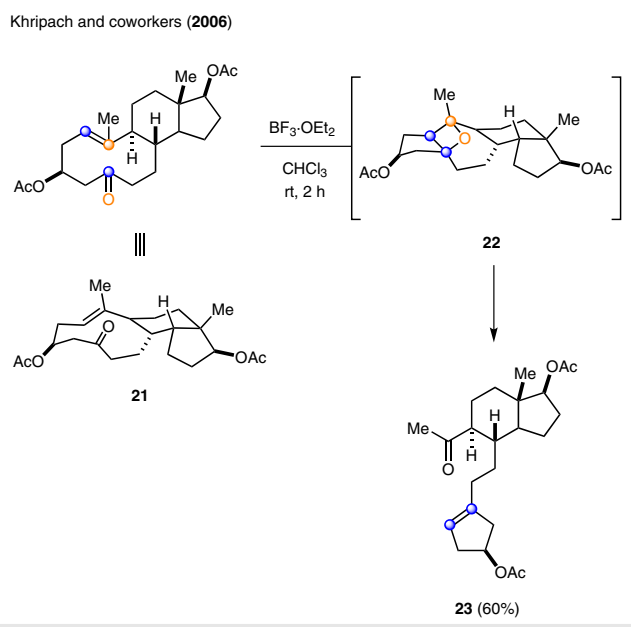
In 1994, Bickelhaupt, van Schaik, and Vijn reported the reaction of benzaldehyde **12** and isobutylene **13** or 2-methyl-2-butene **15** to form styrene (**14**) and β-methylstyrene (**16**) in 15% and 30%, respectively, as the carbonyl–olefin metathesis products (Scheme 3).[9] The reaction is promoted by EPZ-10,[10] a solid Lewis acid catalyst consisting of clay-supported $ZnCl_2$ ($ZnCl_2$ content 12%). Importantly, higher conversion was observed at elevated temperatures and longer reaction times, however, it was accompanied by increased byproduct formation.




**Scheme 3** Carbonyl–olefin metathesis of benzaldehyde using the solid Lewis acid EPZ-10

The authors propose a stepwise mechanism proceeding via initial Lewis acid activation of the carbonyl oxygen in **12** and subsequent nucleophilic addition of olefin **15** to form carbocation **18**. Oxetane **19** results from an intramolecular addition, followed by a Lewis acid assisted fragmentation to yield the carbonyl–olefin metathesis product β-methylstyrene **16**. Importantly, Bickelhaupt and coworkers report the reaction to be limited to carbonyl compounds lacking α-hydrogen substituents which result in competing aldol condensation reactions with the acetone byproduct formed in the carbonyl–olefin metathesis reaction.

Efforts undertaken by Khripach and coworkers to protect the carbonyl moiety in seco-steroid **21** as a dithioketal upon treatment with three equivalents of $BF_3{\cdot}OEt_2$ resulted in the formation of the carbonyl–olefin metathesis product **23** in 60% yield (Scheme 4).[11] Subsequent investigations by Khripach and coworkers showed that the corresponding Z-olefin analogue of **21** failed to undergo carbonyl–olefin metathesis under otherwise identical reaction conditions. An intramolecular, Lewis acid promoted [2+2] cycloaddition and immediate cycloreversion of the resulting oxetane **22** was suggested as a mechanistic hypothesis for the formation of cyclopentene **23**.



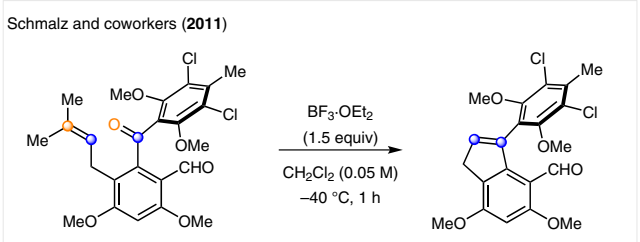

**Scheme 4** Carbonyl–olefin metathesis of 3β,17β-diacetoxy-5,10-secoandrost-1(10)-en-5-one (**21**) upon treatment with $BF_3{\cdot}OEt_2$

During their studies towards the marine natural product pestalone, Schmalz and coworkers observed the formation of indene **25** as a byproduct in 20% yield, upon deprotection attempts of the methylether subunits in *ortho*-prenylated benzophenone **24** (Scheme 5).[12] Subsequent efforts resulted in improved reaction conditions which formed the carbonyl–olefin metathesis product **25** in 87% yield upon treatment with 1.5 equivalents of $BF_3{\cdot}OEt_2$. The generality of this protocol for carbonyl–olefin metathesis was later investigated for a series of acetophenones, bearing prenyl (**26**), geranyl (**28**), and homoprenyl (**29**) sidechains in the *ortho* position. When these substrates were subjected to the optimized reaction conditions relying on 1.5 equivalents of $BF_3{\cdot}OEt_2$ in dichloromethane at –40 °C for one hour, the corresponding indene **27** was formed in 87% and 38% yield, respectively, from acetophenones **26** and **28**. Importantly, the dihydronaphthalene **30** was obtained in 75% yield in a carbonyl–olefin metathesis reaction to form a six-membered ring system.

Schmalz and coworkers also favor a stepwise mechanistic pathway, proceeding via initial *exo*-trig cyclization of **31** upon Lewis acid activation of acetophenone **26** with $BF_3{\cdot}Et_2O$ (Scheme 6). The resulting tertiary carbocation **32** is presumed to isomerize to the more stable benzylic carbocation **34** via intermediate oxetane **33**. Fragmentation of carbocation **34** upon the loss of acetone as byproduct results in the formation of indene **27** as the desired carbonyl-olefin metathesis product.

## 2 Lewis Acid Catalyzed Carbonyl–Olefin Metathesis

Franzén and coworkers were able to build on the results obtained previously by Bickelhaupt and developed an organocatalytic carbonyl–olefin metathesis approach to *trans*-β-alkylstyrenes relying on trityl tetrafluoroborate ($TrBF_4$) as a catalyst.[13] The authors reasoned that the carbocation-based Lewis acid catalyst $TrBF_4$ **37** has the potential to exhibit distinct reactivity compared to metal- or metalloid-based Lewis acid catalysts. Further efforts led to optimized reaction conditions for the carbonyl–olefin metathe-




| entry | substrate | product | yield (%) |
|---|---|---|---|
| 1 | **26** | **27** | 87 |
| 2 | **28** | **27** | 38 |
| 3 | **29** | **30** | 75 |

***Conditions:*** $BF_3{\cdot}OEt_2$ (1.5 equiv), $CH_2Cl_2$ (0.05 M), –40 °C, 1 h.

**Scheme 5** $BF_3$-Promoted intramolecular arbonyl–lefin metathesis of *ortho*-prenylaryl ketones

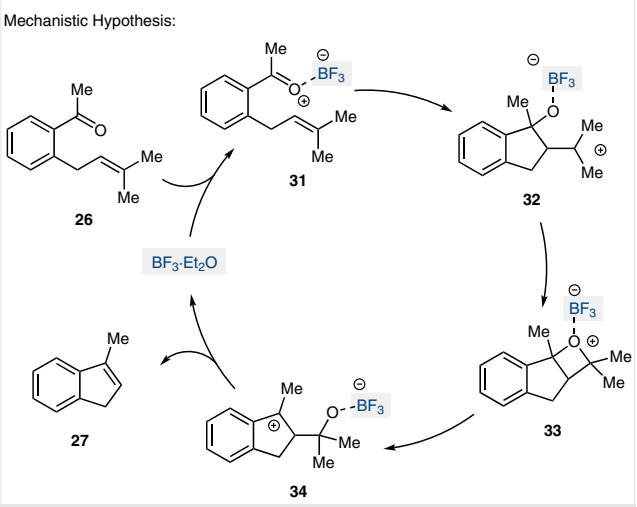
sis of aromatic aldehydes **35** and trisubstituted alkenes **36** relying on 20 mol% $TrBF_4$ **37** as catalyst to result in the formation of *trans*-β-alkylstyrenes in up to 85% yield (Scheme 7).

Though a remarkable advance, the reaction does require the addition of the carbonyl substrate in large access (5:1 ratio) compared to the olefin starting material and long reaction times of up to four days. Weakly electron-withdrawing groups (F, Cl, Br) as well as weakly electron-donating groups (Me, Ar) were tolerated well under the reaction conditions, however, stronger electron-donating aromatic substituents (e.g., MeO) resulted in low yields of the *trans*-β-alkylstyrene products. Additionally, aliphatic aldehydes and tetrasubstituted alkenes were found unreactive under the optimized reaction conditions.

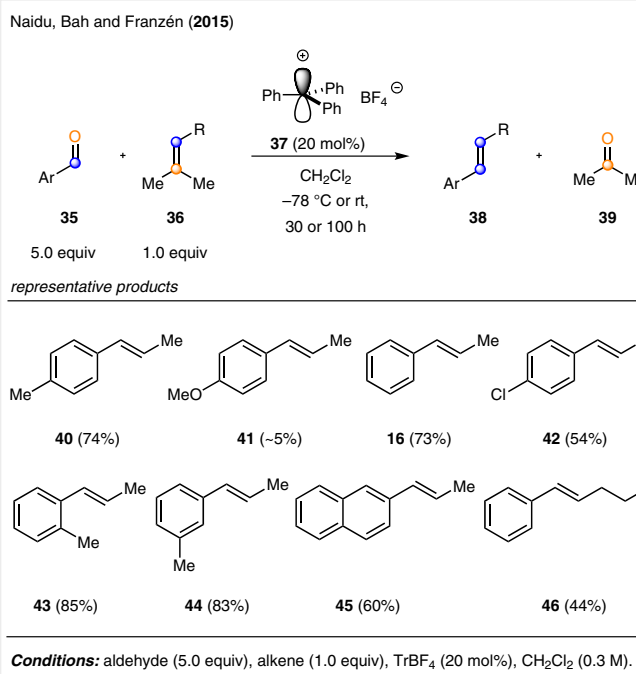
Importantly, Franzén and coworkers also evaluated metal-based Lewis acids for their ability to catalyze the carbonyl–olefin metathesis of aromatic aldehydes **25** and amylene analogues **36**. Zn(II) salts and $SnCl_4$ were found inactive under the reaction conditions, while low yields of the desired products were observed with $InCl_3$ and $AlCl_3$. Notably, $BF_3{\cdot}OEt_2$ and $HBF_4{\cdot}OEt_2$ promoted the formation of *trans*-β-alkylstyrenes **38** in 41% and 44% yield, respectively.

The authors propose a mechanism relying on a stepwise [2+2] cycloaddition pathway to form an intermediate oxetane **49** which subsequently fragments to yield the desired carbonyl–olefin metathesis product (Scheme 8). Upon activation of aldehyde **12** with the Lewis acid **37**, oxonium ion **47** is formed, which can be subsequently attacked by alkene **36** to form the tertiary carbocation **48**. Oxetane **49** results upon intramolecular nucleophilic addition as the product of a formal [2+2] cycloaddition reaction. This reactive intermediate can undergo final Lewis acid promoted fragmentation to yield *trans*-β-alkylstyrene **16** and acetone as the corresponding carbonyl–olefin metathesis products.

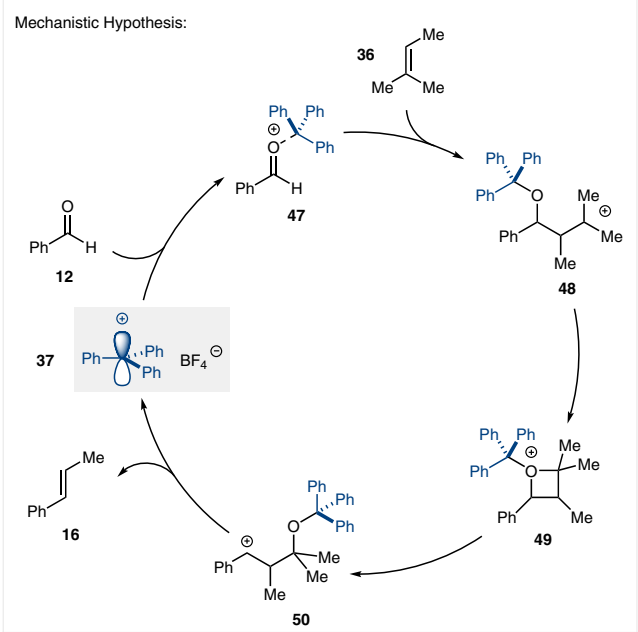
In 2015, our laboratory was able to contribute to this growing area of research by developing a catalytic, carbonyl–olefin ring-closing-metathesis reaction for a variety of aryl ketones. Building on the earlier reports of Bickelhaupt, Khripach, and Schmalz, relying on stoichiometric amounts of Lewis acids, we envisioned an efficient reaction design




**Scheme 6** Mechanistic hypothesis for the $BF_3{\cdot}Et_2O$ promoted formation of indene **27** from acetophenone derivative **26**.

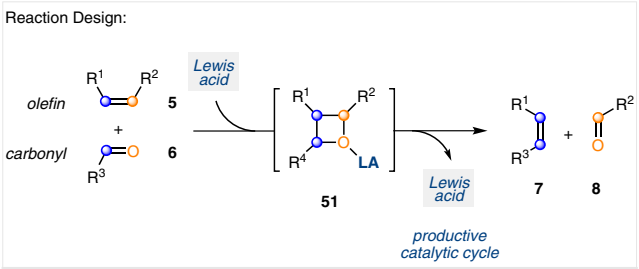



**Scheme 7** Organocatalytic carbonyl–olefin metathesis resulting in *trans*-β-alkylstyrenes




**Scheme 8** Trityl cation-catalyzed carbonyl-olefin metathesis

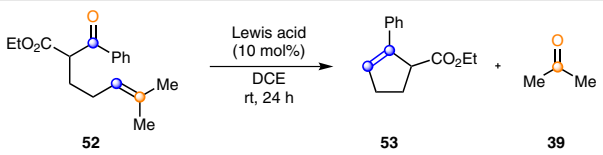
for carbonyl–olefin metathesis. Upon activation with a suitable Lewis acid, carbonyl derivatives **6** and alkenes **5** are able to undergo in situ formation of oxetanes **51** as reactive intermediates, which subsequently fragment to the corresponding carbonyl–olefin metathesis products **7** and **8**, thus allowing for catalyst turnover (Scheme 9).[14] Many challenges are associated with implementing this type of design principle for catalytic carbonyl–olefin metathesis. Specifically, a catalyst capable of promoting both the [2+2] cycloaddition, as well as the subsequent [2+2] cycloreversion, needs to be identified. Additionally, minimizing potential side reactions after [2+2] cycloreversion, such as polymerization and regeneration of starting materials, is important for an efficient reaction protocol. In addition to side reactions, control of chemoselectivity is vital because unsaturated ketone substrates are known to undergo many different Lewis acid mediated reactions, including carbonyl–ene, Prins, and enolate alkylations. We envisioned that the judicious choice of a metal-derived Lewis acid could address these challenges and function as an efficient activator for both oxetane formation and cycloreversion to provide carbonyl–olefin metathesis products. To identify a single Lewis acid capable of catalyzing the desired transformation, we initially investigated the reaction of β-keto ester **52** with various Lewis acids (Scheme 10). Overall, we found $FeCl_3$ (Scheme 10, entry 1) to be the best catalyst for this reaction.




**Scheme 9** Design principle for Lewis acid catalyzed carbonyl–olefin ring-closing metathesis

Lowering the oxidation state of iron from iron(III) to iron(II) results in no conversion (Scheme 10, entry 3), which could be a result of $FeCl_2$ having low solubility in dichloroethane. $FeBr_3$, $GaCl_3$, and $BF_3{\cdot}OEt_2$ (Scheme 10, entries 5, 6, and 8) all provide the desired metathesis product, albeit in lower yield than $FeCl_3$. Considering the demonstrated potential for metal salts to contain catalytically relevant impurities, it was important to determine whether or not $FeCl_3$ was functioning as the active catalytic species.

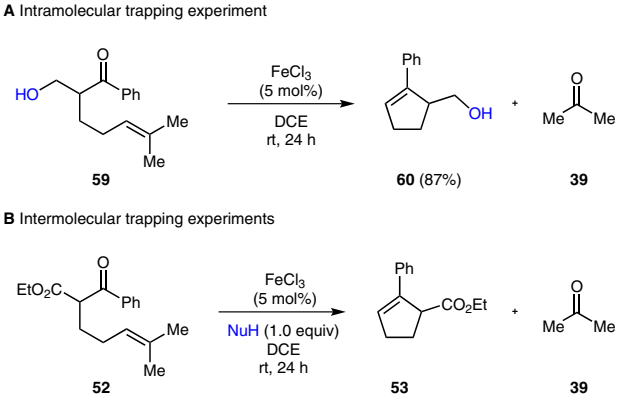
When commercially available, sublimed grade $FeCl_3$ (>99% trace metal basis) was used under otherwise identical reaction conditions, the quantitative formation of **53** was observed (Scheme 10, entry 11), matching the result obtained with reagent grade $FeCl_3$ and validating $FeCl_3$ as the active catalyst in this transformation. Finally, Brønsted




| entry | Lewis acid (10 mol%) | **53** (% yield) | conversion (%) |
|---|---|---|---|
| 1 | $FeCl_3$ | 99 | 100 |
| 2 | $FeCl_3{\cdot}6H_2O$ | 96 | 98 |
| 3 | $FeCl_2$ | 0 | 0 |
| 4 | $Fe(OTf)_3$ | 13 | 22 |
| 5 | $FeBr_3$ | 56 | 62 |
| 6 | $GaCl_3$ | 55 | 53 |
| 7 | $Sc(OTf)_3$ | 19 | 19 |
| 8 | $BF_3{\cdot}Et_2O$ | 71 | 86 |
| 9 | $InCl_3$ | 27 | 27 |
| 10 | $ZnBr_2$ | 0 | 0 |
| 11 | $FeCl_3$ (>99% trace metal basis), sublimed grade | 99 | 100 |
| 12 | pTsOH | 0 | 0 |
| 13 | HCl | 0 | 0 |

***Conditions:*** all reactions were performed using 0.18 mmol β-keto ester **52**, 0.018 mmol Lewis acid in dichloroethane (0.1 M) at room temperature for 24 hours.

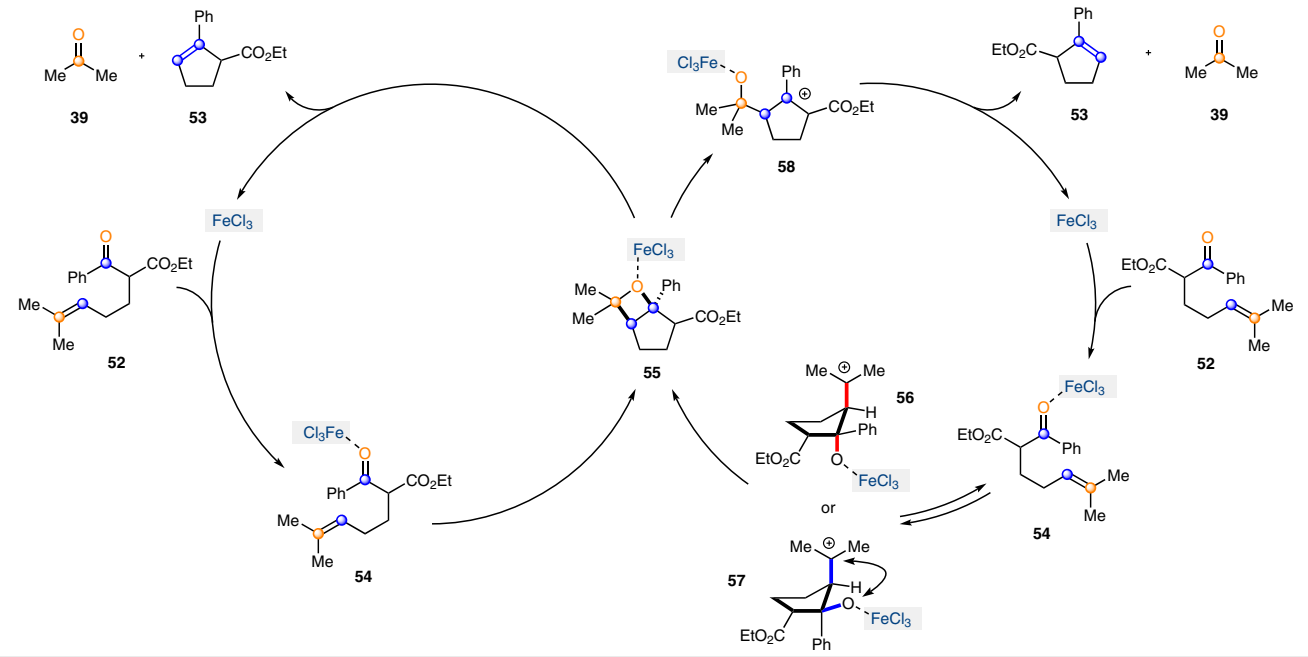
**Scheme 10** Evaluation of various Lewis acids and Brønsted acids in the catalytic carbonyl–olefin ring-closing metathesis of **52**




| entry | NuH | **53** (% yield) | conversion (%) |
|---|---|---|---|
| 1 | methanol | 54 | 56 |
| 2 | isopropanol | 46 | 54 |
| 3 | acetic acid | 98 | 100 |
| 4 | benzoic acid | 94 | 100 |
| 5 | nitromethane | 99 | 100 |
| 6 | acetonitrile | 18 | 20 |

***Conditions:*** all reactions were performed using 0.18 mmol β-keto ester **52**, 0.009 mmol Lewis acid in dichloroethane (0.1 M) at room temperature for 24 hours.

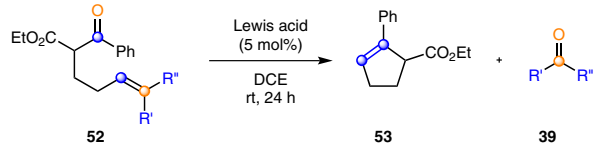
**Scheme 11** Intramolecular and intermolecular trapping experiments of the iron(III)-catalyzed carbonyl–olefin metathesis reaction

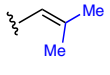
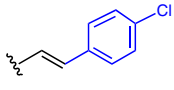
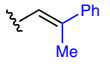
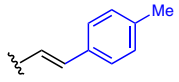
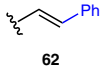
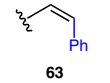
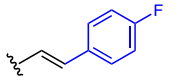



**Scheme 12** Possible mechanistic pathways for the iron(III)-catalyzed carbonyl-olefin metathesis reaction

acids (Scheme 10, entries 12 and 13) did not provide any conversion to the metathesis product, showing that metal-based Lewis acids are uniquely suited to serve as catalysts for this transformation.

Additional efforts focused on mechanistic experiments to trap potential carbocation intermediates. Substrate **59** bearing a pendant alcohol with the potential to trap a benzylic carbocation intermediate **58** resulted in the isolation of the corresponding metathesis product **60** in 87% yield as a single product (Scheme 11). The iron(III)-catalyzed carbonyl–olefin metathesis reaction of **52** has also been conducted under the optimized reaction conditions with the addition of equimolar amounts of various nucleophiles (methanol, isopropanol, benzoic acid, acetic acid, nitromethane, and acetonitrile, Scheme 11, entries 1–6) which have the potential to trap carbocation intermediates as the corresponding nucleophilic addition or subsequent elimination products. The desired carbonyl–olefin metathesis product **53** was isolated as the sole product in all cases in up to 98% yield. No formation of products resulting from intermediate carbocations was observed. The mechanism of this reaction was further studied computationally, using the ZStruct method.[15] This method identified one highly favorable route from starting material to product, involving a concerted, asynchronous [2+2] cycloaddition between the alkene and the carbonyl to give an oxetane and a concerted, asynchronous oxetane cycloreversion to give the desired metathesis product together with the carbonyl byproduct. We initially considered two possible mechanistic scenarios




| entry | alkene | **53** (% yield) | entry | alkene | **53** (% yield) |
|---|---|---|---|---|---|
| 1 |  **52** | 99% | 5 |  **64** | 60% |
| 2 |  **61** | 49% | 6 |  **65** | 62% |
| 3 |  **62** | 60% | | | |
| 4 |  **63** | 49% | 7 |  **66** | 70% |

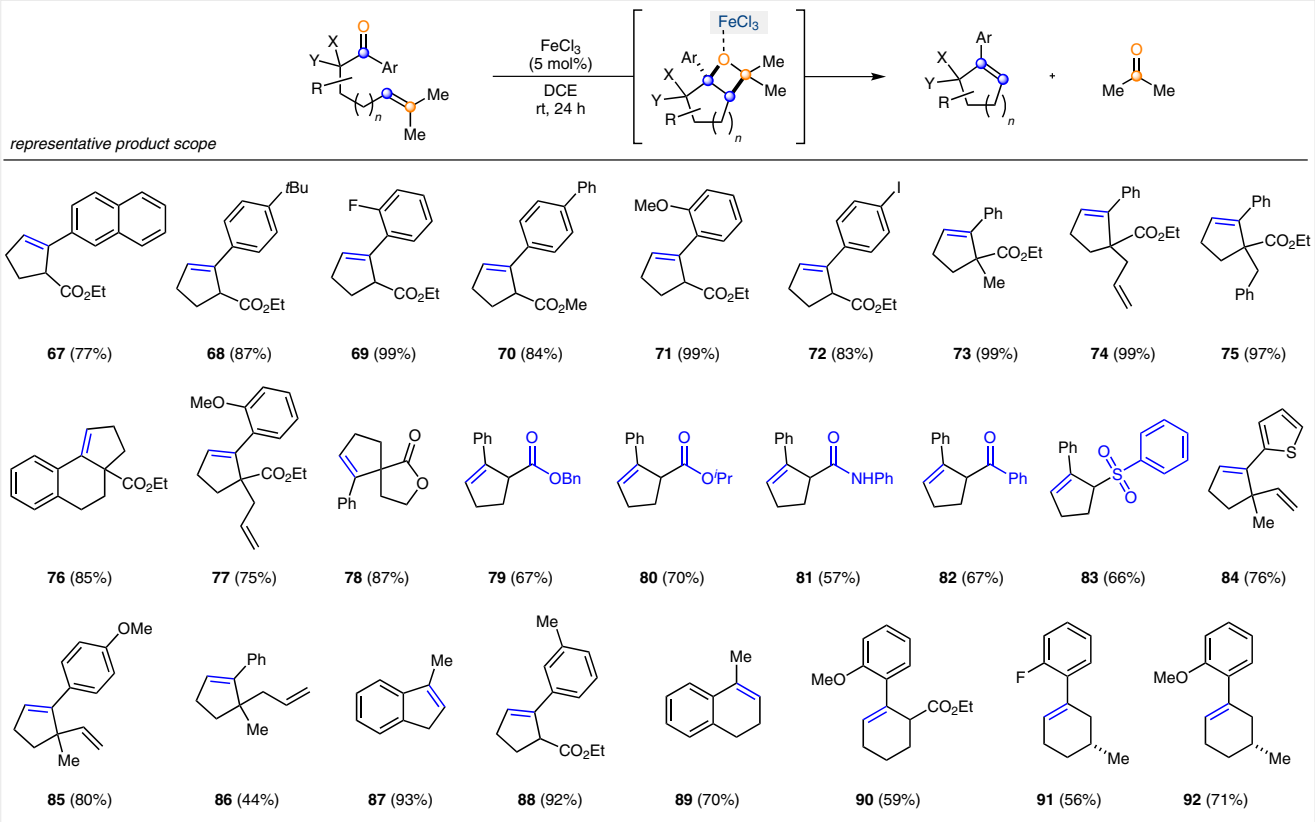
***Conditions:*** ketone (**52**, **61**–**66**, 1.0 equiv), $FeCl_3$ (5 mol%), 0.01M in dichloroethane at room temperature. **63**–**65** were run at reflux.

**Scheme 13** Reactivity of distinct alkene substituents in the iron(III)-catalyzed carbonyl–olefin metathesis reaction

that both utilize oxetane **55** as a key intermediate. The pathway relying on carbocation intermediates (Scheme 12, right) starts with coordination of ketone **52** to $FeCl_3$ resulting in intermediate **54** that is activated for nucleophilic addition by the nearby alkene to result in diastereomeric carbocations **56** and **57**. Ring closure to oxetane **55** is feasible for carbocation **57** but geometrically difficult for **56**, and it is therefore plausible that the two diastereomers interconvert through activated ketone **54**, an explanation that is validated by the high yields observed in many cases. Ring opening of **55** provides benzylic carbocation **58**, which can fragment to produce metathesis product **53** and carbonyl byproduct **39**. Alternatively, a concerted reaction pathway (Scheme 12, left) relies on an iron-mediated [2+2] cycloaddition to provide oxetane **55** that then endures a [2+2] cycloreversion to form metathesis product **53** and carbonyl byproduct **39**. Taken together, the carbocation-trapping experiments and computational investigations point towards a concerted yet asynchronous reaction pathway where carbocation intermediates are not essential for catalysis.

Subsequent investigation of the substrate scope revealed that a variety of aryl substituted alkene substrates **52** afford the expected metathesis product **53** and the corresponding benzaldehyde or acetophenone byproducts **39** (Scheme 13). All alkenes bearing aryl substituents resulted in diminished yields as compared to the dimethyl-substituted alkene, a result that can be explained as an increased stabilization of positive charge leading to less efficient reactivity. Importantly, both (*E*)- **62** and (*Z*)-styrenes **63** convert into cyclization product **53** showing that either alkene stereoisomer is a viable substrate.

Additional investigation of the substrate scope focused on arene substituents, β-substitution, and chain length. Aryl ketones bearing distinct substituents resulted in good yields of the desired metathesis products (Scheme 14, **67**–**72**). Substrates incorporating α-quaternary carbon centers cyclize to the corresponding metathesis products **73**–**78** with remarkable efficiency. Additionally, a plethora of β-substituents are compatible with the optimized reaction conditions for carbonyl–olefin ring-closing metathesis to result in the formation of products containing ester (**79**, **80**), amide (**81**), aryl ketone (**82**), and sulfone (**83**) frag-



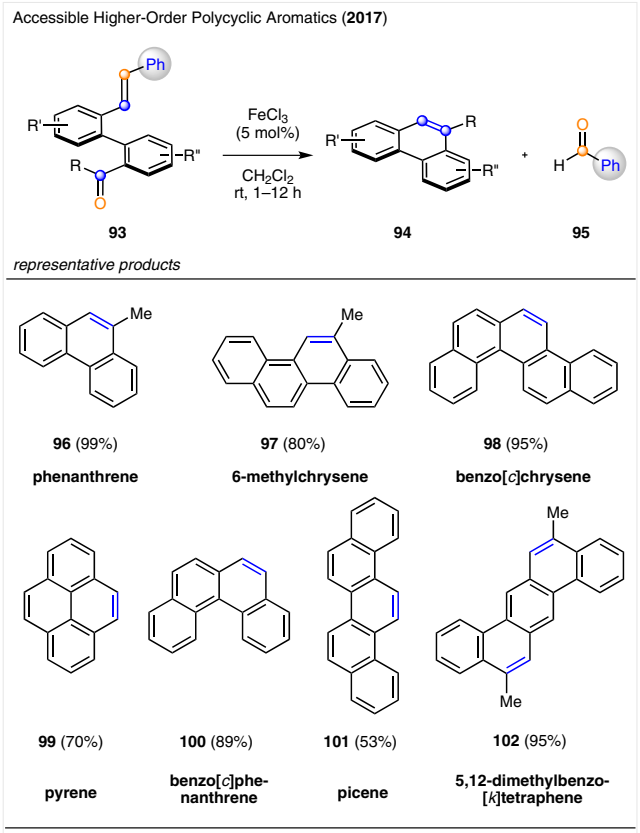

***Conditions:*** ketone (1.0 equiv), $FeCl_3$(5 mol%) in dichloroethane (0.01M) at room temperature. **81** was stoichiometric in $FeCl_3$. For **87**, the yield was determined by gas chromatography analysis using dodecane as an internal standard. For **89**, the yield was determined by $^1$H-NMR analysis using naphthalene as an internal standard. **90** and **91** were run at 60 °C for 12 h. **92** was obtained as a mixture of alkene isomers. X: H, alkyl, aryl, allyl; Y: H, $CO_2R$, $SO_2Ar$, CONHAr; R = H, alkyl; n = 1,2.

**Scheme 14** Representative product scope of the iron(III)-catalyzed carbonyl–olefin ring-closing metathesis reaction

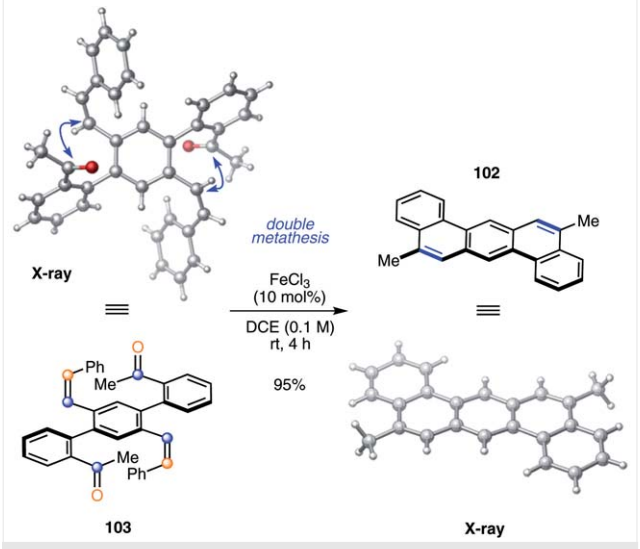
ments. Metathesis products **84**–**87** stem from substrates lacking a 1,3-dicarbonyl functionality, ultimately establishing that this moiety is not necessary for the carbonyl–olefin metathesis reaction to proceed. Finally, homologation of the alkyl chain enables access to cyclohexenes **89**–**92**. Collectively, these examples demonstrate that the iron-catalyzed carbonyl–olefin metathesis reaction is general and highly tolerant of a variety of functional groups.

After developing the carbonyl–olefin metathesis reaction for the synthesis of functionalized cyclopentenes and cyclohexenes, we became interested in applying this process to the synthesis of polycyclic aromatic compounds (PACs).[16] PACs represent important structural motifs in materials science, natural product synthesis, and asymmetric catalysis. The optimized conditions for iron(III)-catalyzed carbonyl–olefin metathesis proved efficient for a wide range of functionalized biaryl ketones **93** to result in the formation of the desired metathesis products **94** in high yields (Scheme 15). Interestingly, while dimethyl-substituted olefins had previously proven superior for the carbonyl–olefin metathesis reaction described above, the styrenyl olefin **93** provided the most efficient conversion into PACs while avoiding carbonyl–ene side reactions. A variety of higher-order polycyclic aromatics is accessible based on this carbonyl–olefin metathesis approach, including benzo[*c*]chrysene **98**, pyrene **99**, and picene **101**. Furthermore, substrate **103**, containing two olefins and two carbonyls, efficiently undergoes a double carbonyl–olefin metathesis reaction to give **102** as the single product in 95% yield (Scheme 16).

Catalytic carbonyl–olefin metathesis reactions have been a long sought after class of transformations in synthetic organic chemistry. Lewis acid mediated approaches to carbonyl–olefin metathesis have seen a progression with early examples, ranging from stoichiometric amounts of Lewis acids and harsh reaction conditions, to intermolecular examples relying on clay-supported Lewis acids resulting in moderate yields of the desired product. The first examples for Lewis acid catalyzed carbonyl–olefin metathesis have recently been developed. Specifically, carbocation-based Lewis acids catalyze the formation of *trans* β-alkylstyrene products in carbonyl–olefin cross-metathesis reactions. The catalytic carbonyl–olefin ring-closing metathesis based on $FeCl_3$ enables efficient access to a variety of five- and six-membered ring systems. The reaction relies on iron as an environmentally benign metal and provides a distinct advance towards the development of a sustainable and economical approach for carbonyl–olefin metathesis. This design principle for iron(III)-catalyzed carbonyl–olefin ring-closing metathesis has already enabled efficient access to a variety of complex molecules, including polycyclic aromatic hydrocarbons which are found as ubiquitous structural motifs in organic and pharmaceutical chemistry as well as materials science.




**Scheme 15** Representative examples of polycyclic aromatics accessible via the iron(III)-catalyzed carbonyl-olefin metathesis




**Scheme 16** Double carbonyl–olefin metathesis approach for the synthesis of 5,12-dimethylbenzo[*k*]tetraphene (**102**)

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