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Catalytic, transannular carbonyl-olefin metathesis reactions†

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Transannular carbonyl-olefin metathesis reactions complement existing procedures for related ring-closing, ring-opening, and intermolecular carbonyl-olefin metathesis. We herein report the development and mechanistic investigation of FeCl_3 -catalyzed transannular carbonyl-olefin metathesis reactions that proceed via a distinct reaction path compared to previously reported ring-closing and ring-opening protocols. Specifically, carbonyl-ene and carbonyl-olefin metathesis reaction pathways are competing under FeCl_3 -catalysis to ultimately favor metathesis as the thermodynamic product. Importantly, we show that distinct Lewis acid catalysts are able to distinguish between these pathways to enable the selective formation of either transannular carbonyl-ene or carbonyl-olefin metathesis products. These insights are expected to enable further advances in catalyst design to efficiently differentiate between these two competing reaction paths of carbonyl and olefin functionalities to further expand the synthetic generality of carbonyl-olefin metathesis.

Introduction

Carbonyl-olefin metathesis reactions represent desirable strategies for catalytic carbonyl olefinations as a result of their potential for direct carbon-carbon bond formation between carbonyl and alkene functionalities.¹ In recent years, distinct classes of catalytic carbonyl-olefin metathesis have been developed to effect ring-closing² (3), ring-opening³ (6) and intermolecular⁴ (8) transformations⁵ (Fig. 1A). We herein report the development of FeCl_3 -catalyzed transannular carbonyl-olefin metathesis (11) that complements existing classes as a fourth, mechanistically distinct reaction category (Fig. 1B). Specifically, in transannular carbonyl-olefin metathesis reactions, carbonyl-ene⁶ and carbonyl-olefin metathesis reaction paths initially compete to ultimately favour the formation of the thermodynamic metathesis product. However, our studies described herein show that distinct Lewis acid catalysts can differentiate between these divergent reaction paths to enable selective access to both products. Furthermore, transannular carbonyl-olefin metatheses are ring-contraction reactions that result in the rapid formation of new and distinct skeletal frameworks. Consequently, these transformations hold great potential for the molecular editing of biologically important natural products and allow access to structurally diverse carbon scaffolds in a single synthetic transformation. Importantly, the concept of molecular editing, “whereby one could selectively insert, delete, or

exchange atoms in highly elaborated molecules”⁷ was recently described as an area of opportunity and high potential impact that is predicted to drive innovation in pharmaceutical drug discovery for the next 50 years. While important advances have already been made that enable the insertion and deletion of atoms in complex molecules via C-H activation approaches,⁸ strategies that allow for a selective exchange of atoms remain rare and represent a challenge for current synthetic chemistry.⁹ We herein show that catalytic, transannular carbonyl-olefin metathesis reactions can contribute to this emerging area of research as transformations that facilitate such a specific exchange. Moreover, distinct Lewis acids enable a divergent and catalyst-controlled strategy for the molecular editing of natural product scaffolds¹⁰ through either carbonyl-olefin metathesis or carbonyl-ene reactions.

Results and discussion

Our studies towards catalytic, transannular carbonyl-olefin metathesis reactions initially required efficient synthetic access to functionalized decalin derivatives (9).¹¹ To assess the potential of this transformation for molecular editing, we developed a short sequence to convert naturally occurring steroids into highly functionalized cyclodecenone systems (Scheme 1, see ESI for details†).¹² Specifically, epoxidation of cholesterol (12), reduction and selective acetylation of the secondary alcohol gave rise to acetate 13. Subsequent Suárez oxidation¹³ with (diacetoxy-iodo)benzene and iodine initiates an alkoxy radical fragmentation to form 14 in 58% yield.

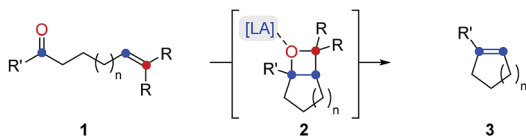
We next focused on the evaluation of distinct Lewis acids to promote transannular metathesis between carbonyl and olefin

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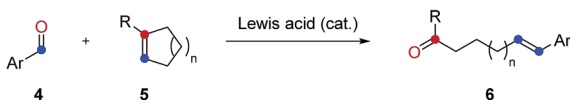
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9sc03716k

A. Established Types of Carbonyl-Olefin Metathesis

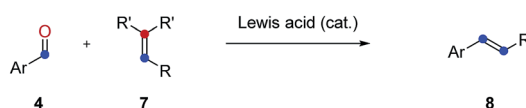
• Ring-Closing Carbonyl-Olefin Metathesis



• Ring-Opening Carbonyl-Olefin Metathesis



• Intermolecular Carbonyl-Olefin Metathesis



B. This work: Transannular Carbonyl-Olefin Metathesis

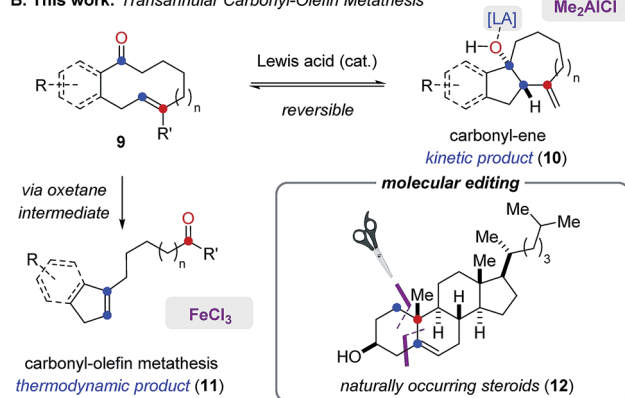
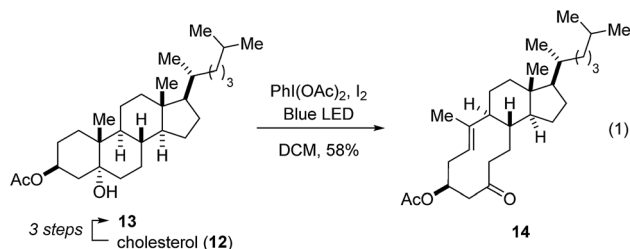


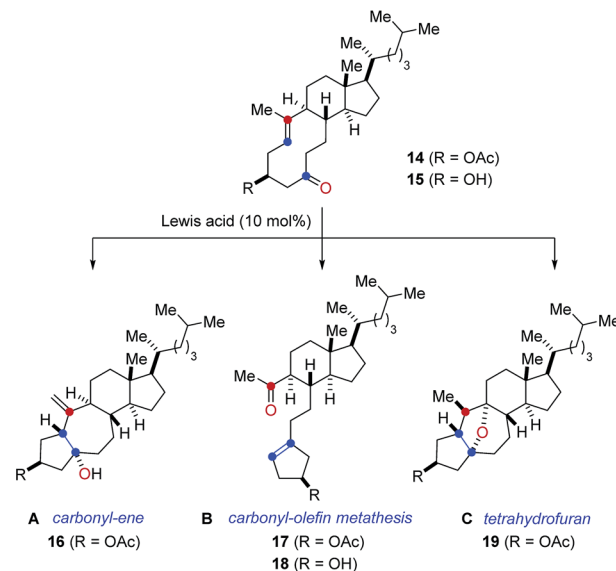
Fig. 1 (A) Established categories of catalytic carbonyl-olefin metathesis reactions. (B) Divergent reactivity of Lewis acids enables transannular carbonyl-olefin metathesis.



Scheme 1 Synthesis of cyclodecenone derivative 14.

functionalities (Fig. 2A). When cyclodecenone **14** was converted with $\text{Sc}(\text{OTf})_3$ as catalyst, the desired metathesis product **17** was isolated in 33% yield together with two additional compounds, subsequently identified as the carbonyl-ene product **16** in 15% yield and tetrahydrofuran **19** in 20% yield (entry 1, Fig. 2A). However, when treated with catalytic amounts of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, the formation of only two distinct products was observed, including metathesis product **17** and tetrahydrofuran **19** in 30% and 23% yield, respectively (entry 2, Fig. 2A). Importantly, stoichiometric amounts of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ¹⁴ also resulted in the formation of both products, albeit in diminished yields of 11% and 25%,

respectively (entry 3, Fig. 2A). Although GaCl_3 was previously identified as a superior Lewis acid for ring-opening carbonyl-olefin metathesis³, catalytic amounts of GaCl_3 failed to promote transannular reactivity of cyclodecenone **14** (entry 4, Fig. 2A). In comparison, 10 mol% SnCl_4 resulted in increased reactivity providing metathesis product **17** in 22% yield and tetrahydrofuran **19** in 44% yield (entry 5, Fig. 2A). Interestingly, when cyclodecenone **15** incorporating a free secondary alcohol was subjected to otherwise identical reaction conditions, the metathesis product **18** was formed exclusively in 65% yield

A. Divergent Reactivity in Lewis Acid-Catalyzed Transformations of **14** and **15**.

entry	Lewis acid	mol%	R	yield A (%)	yield B (%)	yield C (%)
1	$\text{Sc}(\text{OTf})_3$	10	OAc	15	33	20
2	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	10	OAc	-	30	23
3	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	100	OAc	-	11	25
4	GaCl_3	10	OAc	-	3	-
5	SnCl_4	10	OAc	-	22	44
6	SnCl_4	10	OH	-	65	-
7	FeCl_3	10	OAc	-	39	31
8	FeCl_3	10	OH	-	75	-
9	TiCl_4	10	OAc	-	-	43
10	Me_2AlCl^a	100	OAc	85	-	-

Conditions: Substrate **14** or **15** (0.11 mmol), Lewis acid (10 mol%) in DCE (0.05M) at room temperature. ^aReaction performed at 0 °C. See Supporting Information for details on recovered starting material.

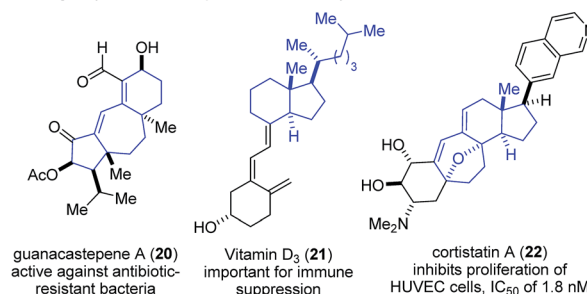
B. Biologically active natural products structurally related to scaffolds **16**, **17**, and **19**.

Fig. 2 (A) Reaction optimization for transannular carbonyl-olefin metathesis. (B) Distinct molecular scaffolds obtained from steroid precursors resemble biologically active molecules.



(entry 6, Fig. 2A). The increased selectivity observed with the free alcohol **15** led us to evaluate additional Lewis acid catalysts. When acetate **14** was converted with catalytic amounts of FeCl_3 , a mixture of both carbonyl-olefin metathesis product **17** and tetrahydrofuran **19** was observed, albeit with increased yields of 39% and 31%, respectively (entry 7, Fig. 2A). However, exclusive formation of the desired carbonyl-olefin metathesis product **18** was observed in superior yields of 75% when cyclodecenone **15** was converted under otherwise identical conditions (entry 8, Fig. 2A).

Subsequent investigations showed that distinct Lewis acids are also capable of promoting the selective formation of either the carbonyl-ene product **16** or tetrahydrofuran **19**. Specifically, 10 mol% TiCl_4 resulted in exclusive formation of tetrahydrofuran **19** in 43% yield, while Me_2AlCl formed the corresponding carbonyl-ene product **18** in 85% yield (entries 9 and 10, Fig. 2A). These results suggest that the appropriate choice of Lewis acid now enables selective access to distinct molecular frameworks and consequently represents an approach for divergent molecular editing *via* transannular reactions between carbonyl and olefin functionalities. Importantly, the resulting diverse molecular scaffolds of the products closely resemble naturally

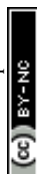
occurring compounds of biological importance, including guanacastepene A (**20**)¹⁵, vitamin D₃ (**21**)¹⁶, and cortistatin A (**22**)¹⁷ (Fig. 2B).

The optimal reaction conditions developed for FeCl_3 -catalyzed, transannular carbonyl-olefin metathesis proved general for a variety of 9- and 10-membered ring systems (Table 1). Unfunctionalized medium-sized rings proved viable substrates for transannular carbonyl-olefin metathesis and resulted in good overall yields. Specifically, cyclodecenone **23** formed the desired metathesis product **24** in 42% yield while differently substituted cyclonononones **25a**, **25b**, and **25c** bearing methyl and bromide substituents resulted in yields of 40–64% (entries 1 and 2, Table 1). To further evaluate the potential of Lewis acid-catalyzed transannular carbonyl-olefin metathesis for the molecular editing of natural products, we subsequently investigated additional naturally occurring steroids. Specifically, cholesterol, stigmasterol, pregnenolone, and dehydroepiandrosterone derived cyclodecenones readily available *via* our synthetic strategy (Scheme 1). Acetate **14** underwent the desired transannular carbonyl-olefin metathesis reaction in 39% yield while the corresponding alcohol **15** resulted in increased yields of 75%. Similarly, stigmasterol-derived cyclodecenones **27** and

Table 1 FeCl_3 -catalyzed transannular carbonyl-olefin metathesis

Entry	Substrate	Product	Entry	Substrate	Product
1			2		
	23	24 (42%)		25a (R = H) 25b (R = 6-Me) 25c (R = 5-Br)	26a (64%) 26b (53%) 26c (40%)
3			5		
4			6		
	14 15	17 (39%) 18 (75%)		27 29	28 (26%) 30 (51%)
7			9		
8			10		
	31 33	32 (69%) 34 (84%)		35 37	36 (46%) 38 (44%)

Conditions: Substrate (0.11 mmol), FeCl_3 (10 mol%) in DCE (0.05M) at room temperature.



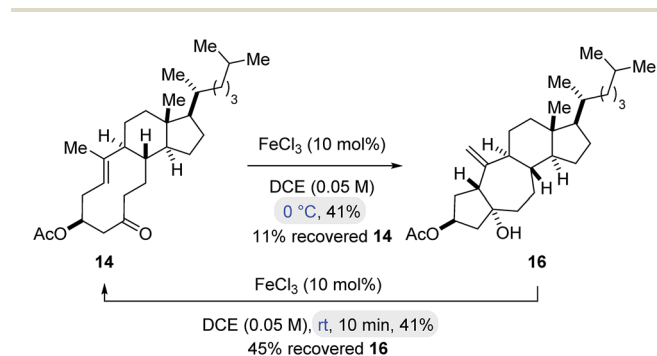
29 resulted in 26% and 51% yield, respectively, when converted with catalytic amounts of FeCl_3 (entries 5 and 6, Table 1). Silyl-ether **31** obtained from pregnenolone formed the desired metathesis product in 69% yield while the corresponding alcohol **33** resulted in 84% yield. Furthermore, cyclodecenones **35** and **37** obtained from naturally occurring dehydroepiandrosterone formed the desired metathesis products **36** and **38** in 46% and 44% yield, respectively (entries 9 and 10, Table 1).

To obtain insights into the controlling features of FeCl_3 -catalyzed transannular carbonyl-olefin metathesis reactions, we conducted additional experimental investigations. We first evaluated the temperature dependence of this transformation (Scheme 2). Surprisingly, when cyclodecenone **14** was converted with 10 mol% FeCl_3 at 0 °C, neither metathesis product **17** nor tetrahydrofuran **19** were obtained; instead, the carbonyl-ene product **16** was isolated in 41% yield along with recovered starting material in 11% yield (Scheme 2). However, when carbonyl-ene product **16** was subjected to the conditions optimized for transannular carbonyl-olefin metathesis (10 mol% FeCl_3 in DCE at room temperature), the formation of cyclodecenone **14** was observed in 41% yield together with recovered starting material **16** in 45% yield, suggesting the reversibility of the carbonyl-ene reaction (Scheme 2). These observations are in stark contrast to results previously obtained in GaCl_3 -catalyzed ring-opening carbonyl-olefin metathesis in which a competing, irreversible carbonyl-ene reaction path is responsible for diminished yields of the metathesis product.³

To further probe this hypothesis suggesting a reaction path for transannular carbonyl-olefin metathesis that is distinct from ring-closing, ring-opening, and intermolecular carbonyl-olefin metathesis, we conducted computational investigations (unrestricted B97-D density functional and 6-31G* basis set).¹⁸ Our studies show that cyclodecenone **14** (ref. 19) can undergo either of two reversible reactions upon binding to FeCl_3 (**14** + Fe, Fig. 3A) leading to oxetane formation *via* an asynchronous, concerted [2 + 2]-cycloaddition that proceeds with an enthalpic barrier of 5.9 kcal mol⁻¹ (**39** + Fe *via* TS-I) or carbonyl-ene reaction that proceeds with a barrier of 14.1 kcal mol⁻¹ (**16** + Fe *via* TS-II) above the substrate complex (**14** + Fe; Fig. 3A). Additionally, our previous experimental results have shown that in comparison to oxetane **39**, only the carbonyl-ene product **16** is stable upon isolation. These observations are supported by

the relative enthalpies of the uncoordinated oxetane **39** (0.2 kcal mol⁻¹), which was found to be higher than the uncoordinated carbonyl-ene product **16** by 13.6 kcal mol⁻¹ and is therefore less stable (Fig. 3). Subsequent efforts focused on investigating the fragmentation of oxetane **39** computationally. Importantly, our investigations revealed two possible paths for oxetane fragmentation; (1) an asynchronous, concerted retro [2 + 2]-cycloaddition proceeds with an enthalpic barrier of 15.1 kcal mol⁻¹ above the iron-substrate complex (**14** + Fe) to form the transannular carbonyl-olefin metathesis product (**17** + Fe, Fig. 4). (2) Alternatively, oxetane **39** can fragment upon elimination to result in cycloheptene (**40** + Fe). This elementary step proceeds with a barrier of 17.9 kcal mol⁻¹ above the substrate complex (**14** + Fe). Notably, this elimination reaction represents an unprecedented mode of Lewis acid-catalyzed oxetane fragmentation. Intramolecular addition of the tertiary alcohol to the alkene moiety results in the formation of the furan byproduct observed under FeCl_3 -catalysis (**19** + Fe, Fig. 4).

Our computational investigations suggest oxetane fragmentation as the rate-limiting steps of both transannular carbonyl-olefin metathesis and furan formation. These results are consistent with our experimental observations as temperatures greater than 0 °C are necessary to afford carbonyl-olefin metathesis product **17** (TS-III, 15.1 kcal mol⁻¹) or furan product **19** (TS-IV, 17.9 kcal mol⁻¹) (Fig. 4).



Scheme 2 FeCl_3 also catalyses a reversible transannular carbonyl-ene reaction.

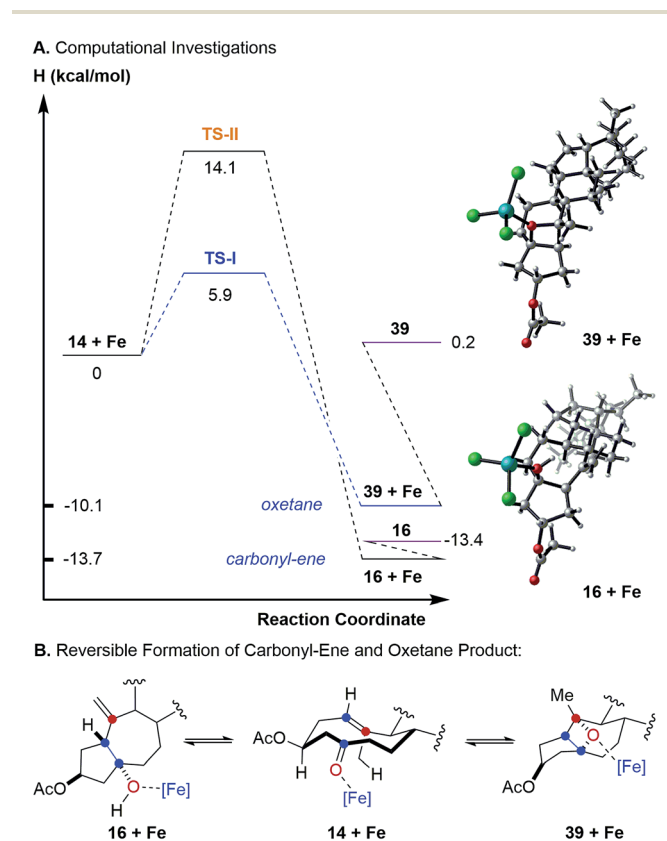


Fig. 3 (A) Computed energies comparing carbonyl-ene and oxetane-forming pathways. (B) Carbonyl-ene reaction and oxetane formation proceed reversibly under FeCl_3 -catalysis in transannular carbonyl-olefin metathesis.

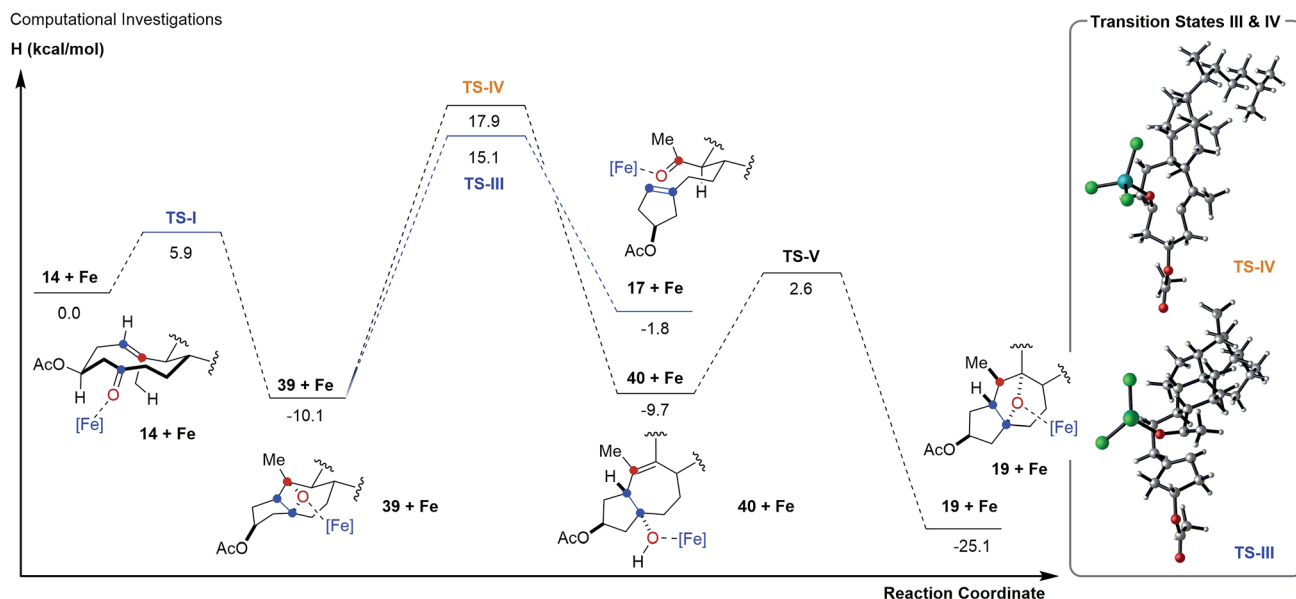


Fig. 4 Reaction path for transannular carbonyl-olefin metathesis and the formation of furans from intermediate oxetanes 39.

Based on our computational and experimental results, we postulate a reaction mechanism for FeCl_3 -catalyzed transannular carbonyl-olefin metathesis that differs from ring-closing, ring-opening, and intermolecular carbonyl-olefin metathesis (Fig. 5). Upon activation with the Lewis acid catalyst, the cyclodecenone substrate 14 can undergo either of two reversible transformations. Specifically, a reversible carbonyl-ene reaction forms the kinetic product 16 while a reversible asynchronous, concerted $[2 + 2]$ -cycloaddition results in oxetane 39 as the thermodynamic product. Importantly, the carbonyl-ene product 16 can be isolated at lower temperatures under otherwise identical reaction conditions as a stable product. In

comparison, our attempts to isolate oxetane 39 were unsuccessful which is corroborated by our theoretical investigations that found the uncoordinated species to be significantly less stable than 16 by $13.6 \text{ kcal mol}^{-1}$. The FeCl_3 -coordinated oxetane can subsequently undergo two distinct fragmentation pathways. Asynchronous, concerted retro $[2 + 2]$ -cycloaddition results in the formation of the desired transannular carbonyl-olefin metathesis product 17. Alternatively, oxetane 39 can undergo a competing FeCl_3 -catalyzed fragmentation *via* elimination to result in the formation of a cycloheptene intermediate (40 + Fe, Fig. 5).²⁰ Subsequent addition of the activated tertiary alcohol to the alkene subunit in 40 gives rise to tetrahydrofuran

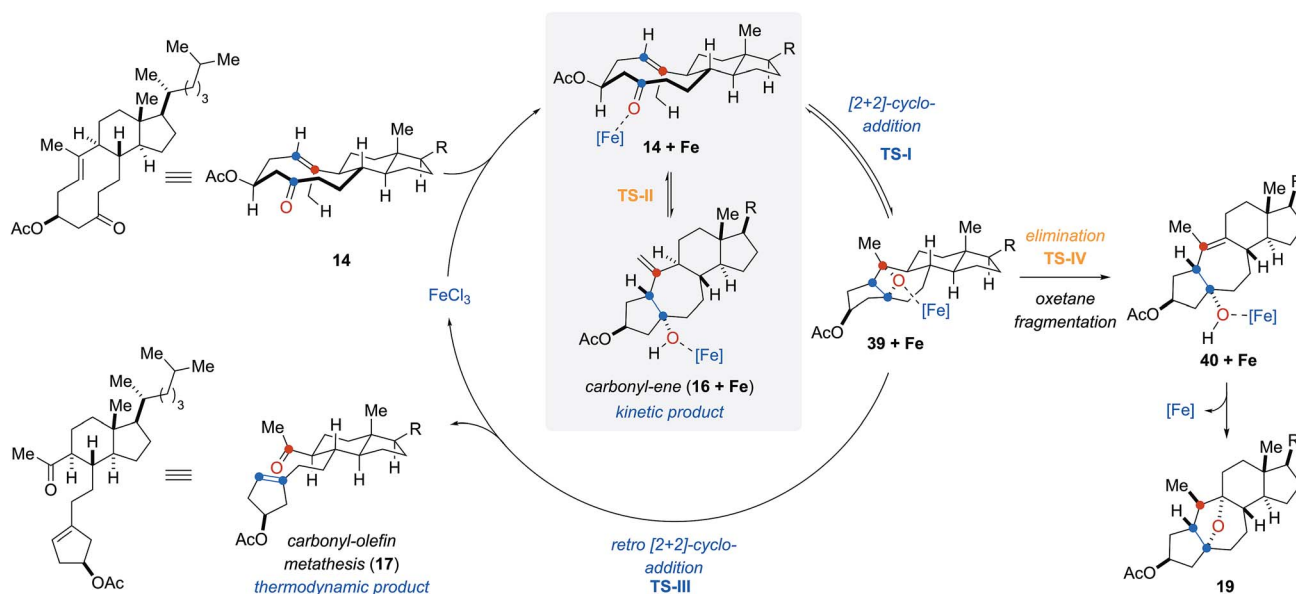


Fig. 5 Mechanistic hypothesis for FeCl_3 -catalyzed transannular carbonyl-olefin metathesis reactions.

19 as the product resulting *via* a distinct mechanism for oxetane fragmentation. Importantly, other Lewis acids can differentiate selectively between these competing reaction paths (see Fig. 2). Specifically, when cyclodecenone **14** is converted with Me_2AlCl as Lewis acid, carbonyl-ene product **16** is isolated exclusively, suggesting that under Me_2AlCl -mediated conditions the carbonyl-ene reaction is not reversible and **16** is formed as the thermodynamic product. Furthermore, when cyclodecenone **14** is reacted with catalytic amounts of TiCl_4 , tetrahydrofuran **19** is

obtained as the sole product, suggesting that the fragmentation of intermediate oxetane **39** proceeds exclusively *via* elimination under these reaction conditions.

Additionally, we observed that the substituents in the 2-position to the reactive carbonyl can affect yield and selectivity of the transannular carbonyl-olefin metathesis reaction (Table 1). We initially hypothesized that hydroxyl functionalities in this position could lead to a reactive conformation that enables bidentate binding of the FeCl_3 catalyst and ultimately favours transannular carbonyl-olefin metathesis. However, our subsequent computational investigations do not provide support for this hypothesis. Based on these results, we favour a revised postulate to explain the origin of this selectivity. Specifically, the Lewis basic acetate functionality is capable of coordinating FeCl_3 bound to the intermediate oxetane (**39** + Fe , Fig. 5), resulting in elongation of one C–O bond and disruption of the retro [2 + 2] pathway (TS-III) to ultimately facilitate the elimination pathway (TS-IV). The inability of free hydroxyl (**15**, **29**, **33**, **37**) or silyl ether (**31**) substrates to afford the tetrahydrofuran product is consistent with this mechanistic proposal. This notable control over selectivity for carbonyl-olefin metathesis is an important observation that we expect to have valuable implications for future catalyst design and development in carbonyl-olefin metathesis reactions, specifically those that are hampered by competing carbonyl-ene and/or oxetane fragmentation paths that do not favour metathesis.

Additionally, the reactivity of the analogous *Z* isomer **Z-14** was investigated (Fig. 6). However, treatment of **Z-14** with catalytic amounts of FeCl_3 under optimal reaction conditions resulted in the exclusive isolation of starting material. Importantly, no formation of carbonyl-ene or carbonyl-olefin

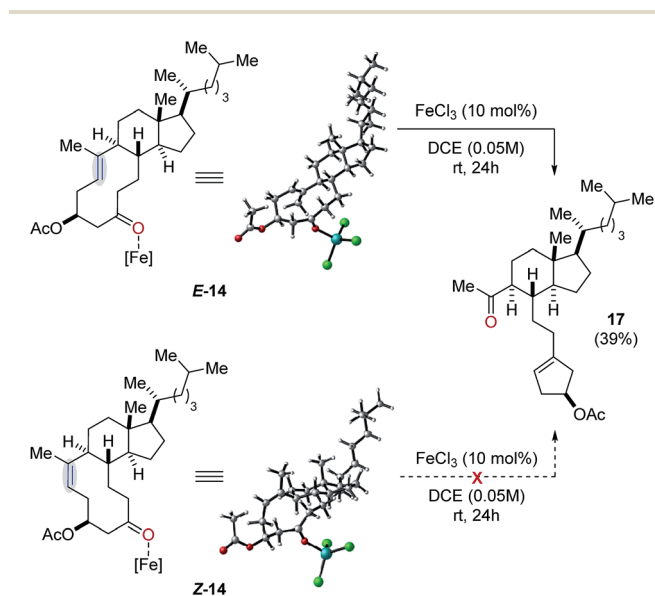


Fig. 6 Comparison of reactivity between *E* and *Z* isomers of cholesterol-derived substrate **14**.

Table 2 Me_2AlCl -mediated transannular carbonyl-ene reactions

Entry	Substrate	Product	Entry	Substrate	Product
1			2		
3			4		

Conditions: Substrate (0.11 mmol), Me_2AlCl (10 mol%) in DCE (0.05M) at 0°C for 1h. *reaction carried out on 0.056 mmol scale at room temperature.



metathesis product was observed which was subsequently supported by computational investigations (Fig. 6). Specifically, we were unable to identify a reactive pathway leading to carbonyl-ene or carbonyl-olefin metathesis formation with resulting energy barriers being prohibitively high at 135.6 kcal mol⁻¹ (see ESI for details†). This lack of reactivity is consistent with high strain being introduced when forming an oxetane intermediate from starting material **Z-14**.

Our investigations next focused on investigating the generality of Me₂AlCl in preferentially promoting transannular carbonyl-ene²¹ over carbonyl-olefin metathesis reaction paths (Table 2). Importantly, when various cyclodecenone substrates were treated with stoichiometric amounts of Me₂AlCl, the formation of the corresponding transannular carbonyl-ene products is observed in all cases in good to excellent yields as the exclusive product. Specifically, cyclodecenone **14** resulted in tetracycle **16** in 85% yield, while stigmasterol-derived substrate **27** resulted in 76% of carbonyl-ene product **39** (entries 1 and 2, Table 2). Similarly, exclusive formation of the corresponding carbonyl-ene products was observed with pregnenolone- and androsterone-derived cyclodecenones **31** and **35** in 73% and 59% yield, respectively (entries 3 and 4, Table 2).

Conclusions

This report describes the development and mechanistic investigation of catalytic, transannular carbonyl-olefin metathesis reactions as a fourth category of these transformations. The mechanism for transannular carbonyl-olefin metathesis is distinct and relies on competing carbonyl-ene and carbonyl-olefin metathesis reaction paths that ultimately favour metathesis as the thermodynamic product. Importantly, distinct Lewis acids are shown to be capable of differentiating between these pathways, providing a new opportunity for the molecular editing of naturally occurring complex molecules. The feasibility of this approach is demonstrated on several complex cyclodecenone systems readily derived from naturally occurring steroids that provide rapid access to three new and distinct molecular scaffolds simply based on the choice of Lewis acid.

Conflicts of interest

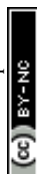
The authors declare no conflicts of interest.

Acknowledgements

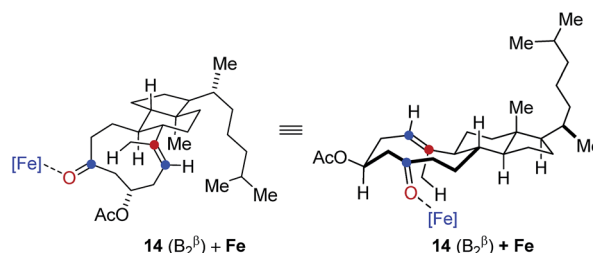
We thank the NIH (R01-GM118644) for financial support. P. S. R. thanks the Rackham Graduate School of the University of Michigan for a dissertation fellowship. C. S. S. thanks the Alfred P. Sloan Foundation, the David and Lucile Packard Foundation, and the Camille Dreyfus Foundation for fellowships. We thank Duncan Ellinwood and Yuan Lu for help with preliminary experiments. We thank Ren Wiscons and Jeff Kampf for X-ray crystallography. We are grateful to Paul Zimmerman and Michael Robo for helpful discussions regarding computational studies.

Notes and references

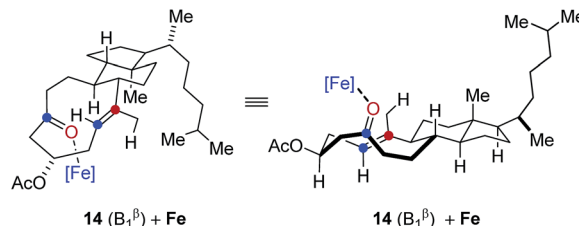
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In comparison, conformation **14** (B_1^β) was found to lead to the preferential formation of diastereomeric product *epi*-**16** that is not observed experimentally under our optimal reaction conditions. See ESI for details.†



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