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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 31 Dec 2018

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Catalytic Carbonyl-Olefin Metathesis of Aliphatic Ketones: Iron(III) Homo-Dimers as Lewis Acidic Superelectrophiles

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Supporting Information Placeholder

ABSTRACT: Catalytic carbonyl-olefin metathesis reactions have recently been developed as a powerful tool for carbon-carbon bond formation. However, currently available synthetic protocols rely exclusively on aryl ketone substrates while the corresponding aliphatic analogs remain elusive. We herein report the development of Lewis acid-catalyzed carbonyl-olefin ring-closing metathesis reactions for aliphatic ketones. Mechanistic investigations are consistent with a distinct mode of activation relying on the *in situ* formation of a homobimetallic singly-bridged iron(III)-dimer as the postulated active catalytic species. These “superelectrophiles” function as more powerful Lewis acid catalysts that form upon association of individual iron(III)-monomers. While this mode of Lewis acid activation has previously been postulated to exist, it has not yet been applied in a catalytic setting. The insights presented are expected to enable further advancement in Lewis acid catalysis by building upon the activation principle of “superelectrophiles” and to broaden the current scope of catalytic carbonyl-olefin metathesis reactions.

Introduction

Carbonyl-olefin metathesis reactions are at the forefront of current research as a result of their potential for direct carbon-carbon bond formation between carbonyl and olefin functionalities. Distinct approaches for carbonyl-olefin metathesis have been advanced relying on stepwise oxetane formation and subsequent fragmentation,¹ the use of molybdenum alkylidenes as reagents,² or bicyclic hydrazine catalysts which enable the first catalytic protocol to effect this transformation.³ Additionally, Lewis acid-catalyzed protocols have recently been developed as a viable reaction design for carbonyl-olefin metathesis.⁴⁻⁶ Upon binding to a Lewis acid catalyst, such as FeCl₃, the carbonyl functionality is activated to perform a [2+2]-cycloaddition forming an intermediate oxetane, which subsequently undergoes a retro-

[2+2]-cycloaddition resulting in the desired metathesis product. While successful protocols for intramolecular and intermolecular Lewis acid-catalyzed carbonyl-olefin metathesis have been reported following this reaction design principle,^{7,8} all current procedures rely exclusively on aryl carbonyls as substrates while the reaction of aliphatic ketones remain elusive.⁴⁻⁸ We report herein the development of a catalytic carbonyl-olefin ring-closing metathesis of aliphatic ketones that proceeds in yields up to 94% and tolerates a variety of functional groups. Mechanistic investigations reveal a distinct mode of activation for aliphatic ketones relative to their aromatic analogs in which the formation of a homobimetallic singly-bridged iron(III)-dimer as the active catalytic species enables the formation of a significantly enhanced electrophilic moiety.

In our initial efforts to develop an FeCl₃-catalyzed carbonyl-olefin metathesis reaction, we had investigated both aryl ketone **1** and aliphatic ketone **4** in their ability to undergo the desired transformation and observed profound differences in reactivity.^{5a} While phenyl ketone **1** leads to carbonyl-olefin metathesis product **2** in 99% yield relying on 5 mol % FeCl₃ as the Lewis acid catalyst (Fig. 1), the corresponding methyl ketone **4** failed to undergo the desired transformation under otherwise identical reaction conditions. As part of our mechanistic investigations towards FeCl₃-catalyzed carbonyl-olefin metathesis reactions,^{5c} we identified three main challenges associated with aliphatic ketones as substrates. 1) In the carbonyl-olefin metathesis reactions of aryl ketones, catalyst turnover is enabled due to the favored binding of the substrate **8** to FeCl₃ by 2.4 kcal/mol in comparison to acetone **6** (Fig. 2A). However, aliphatic ketones (**7**) bind less strongly to the FeCl₃ catalyst by ~1 kcal/mol as

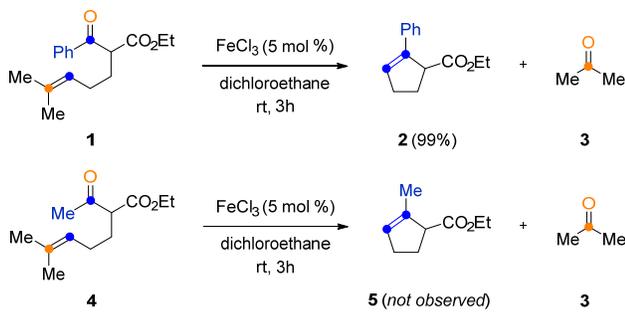


Figure 1. Comparison of aryl ketones and aliphatic ketones in FeCl₃-catalyzed carbonyl-olefin metathesis.

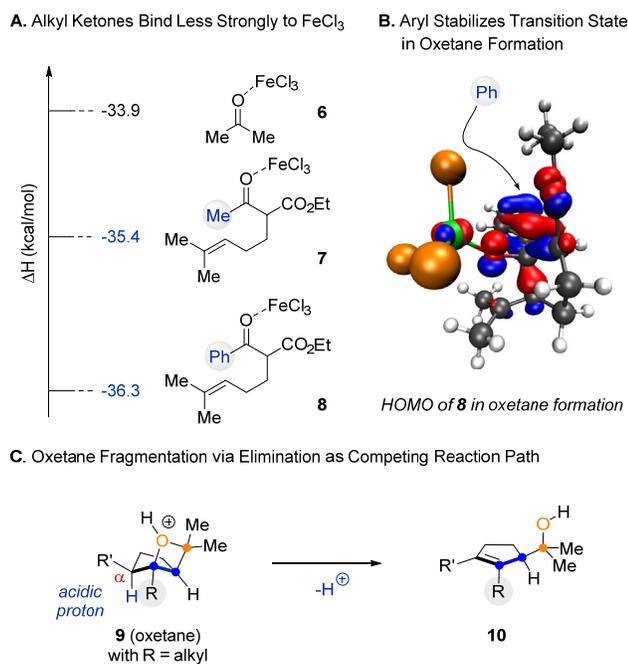


Figure 2. Challenges associated with aliphatic ketones in catalytic carbonyl-olefin metathesis reactions.

compared to their aromatic analogs (**8**) thereby requiring stronger Lewis acids to efficiently activate these less reactive substrates for carbonyl-olefin metathesis (Fig. 2A). Additionally, competitive binding of the Lewis acid with the acetone by-product **3** is more prominent for aliphatic ketones and catalyst inhibition becomes a concern. 2) Our mechanistic investigations identified the aromatic moiety of aryl ketones as a required structural component that plays a crucial role in transition state stabilization^{5c} by redistributing electron density (**8**, Fig. 2B).

Table 1. Lewis acid evaluation in the carbonyl-olefin metathesis of aliphatic ketone **11**.

entry	Lewis acid	mol %	solvent	time (h)	yield 12 (%)	conv. (%)
1	AlCl ₃	5	DCE	24	0	0
2	TiCl ₄	5	DCE	24	0	36
3	GaCl ₃	5	DCE	16	21	82*
4	BF ₃ ·OEt ₂	5	DCE	24	24	51
5	SnCl ₄	5	DCE	24	30	70*
6	EASC	100	DCE	16	30	100*
7	FeCl ₃	5	DCE	15 min	44	48
8	FeCl ₃	10	DCE	15 min	68	70
9	FeCl ₃	10	DCE	3	74	78
10	FeCl ₃	5	DCM	24	37	40
11	FeCl ₃	5	toluene	24	0	25
12	HCl	5	DCE	24	0	7
13	TfOH	5	DCE	24	0	3
14	H ₂ SO ₄	5	DCE	24	0	93*

Conditions: All reactions were performed using 0.16 mmol of ketone **11** and Lewis acid in solvent (0.05 M) at 23 °C. EASC = ethyl aluminum sesquichloride.*Substrate decomposition was observed.

3) Recent investigations of Brønsted acid-catalyzed oxygen atom transfer reactions have shown that alternate oxetane fragmentation pathways exist competing with carbonyl-olefin metathesis reactions.⁹ Specifically, acidic protons in the α -position to the carbonyl functionality can engage in distinct oxetane fragmentation pathways under acid-catalyzed conditions forming the corresponding unsaturated alcohols **10** via elimination (Fig. 2C).¹⁰ On the basis of the identified challenges, we expected aliphatic ketones to require activation by a Lewis acid far exceeding the strength of FeCl₃. Additionally, we switched from β -ketoester **4** bearing an acidic α -proton to methyl ketone **11** incorporating an α -quaternary carbon as a substrate for the evaluation of distinct Lewis acids to avoid competing oxetane fragmentation pathways (Table 1).

Results and Discussion

Our initial efforts focused on the evaluation of more powerful Lewis acids compared to FeCl₃ upon conversion with aliphatic ketone **11**. However, using substoichiometric amounts of the strong Lewis acid, AlCl₃, no formation of the desired metathesis product **12** was observed (entry 1, Table 1). Nevertheless, the use of stoichiometric amounts of the strong Lewis acid ethyl aluminum sesquichloride (EASC) resulted in the formation of **12** in 30% yield and with complete consumption of substrate **11** (entry 6, Table 1). Control reactions with weaker Lewis acids, including SnCl₄ and GaCl₃ also resulted in the formation of the desired cyclopentene **12**, albeit in low yields of 30% and 21%, respectively, and increased decomposition of starting material (entries 3 and 5, Table 1). Similarly, BF₃·Et₂O formed the desired product in 24% while TiCl₄ failed to provide cyclopentene **12** under otherwise identical reaction conditions. Based on this range of reactivities observed with Lewis acids varying in strength, we investigated varying amounts of FeCl₃ upon conversion with methyl ketone **11**. Surprisingly, formation of metathesis product **12** was observed in yields of up to 44% with an abbreviated reaction time of 15 minutes, in comparison to 16 to 24 hours with other Lewis acids (entry 7, Table 1). Increasing catalyst loading to 10 mol % FeCl₃ proved beneficial and resulted in improved yields of 68% within 15 minutes (entry 8, Table 1). Further efforts identified conducting the reaction for 3 hours as optimal, resulting in 74% yield of metathesis product **12** and 78% conversion of starting material **11** (entry 9, Table 1). In ensuing attempts to further optimize this transformation, we observed a decreased yield of 37% when the reaction was conducted in dichloromethane as solvent under otherwise identical reaction conditions (entry 10, Table 1). Furthermore, no formation of the desired metathesis product **12** was detected using toluene as the reaction solvent. Both of these results are in stark contrast to carbonyl-olefin metathesis reactions of aryl ketones which tolerate chlorinated hydrocarbon solvents as well as aromatic solvents.^{5a,c} Less than stoichiometric amounts of Brønsted acids including HCl, TfOH, and H₂SO₄ did not result in the formation of the desired carbonyl-olefin metathesis product **12** (entries 12-14, Table 1). Interestingly, the results obtained relying on FeCl₃ as optimal Lewis acid catalyst did not corroborate our preceding theoretical investigations focused on enthalpies for Lewis acid activation that predict the need for a more potent Lewis acid to effectively activate aliphatic ketones (Fig. 2).

We next explored the effect of varying alkene substitution in the iron (III)-catalyzed carbonyl-olefin metathesis reaction of aliphatic ketones. While ketone **11a** bearing a prenyl fragment

Table 2. Evaluation of olefin substitution in the carbonyl-olefin metathesis of aliphatic ketones **11a-f**.

entry	olefin	yield (%)	entry	olefin	yield (%)
1		74%	4		5% ^a
2		77% ^a	5		30% ^a
3		78% ^a	6		25% ^a

Conditions: All reactions were performed using 0.5 mmol of ketone **11a-f** and 0.05 mmol of FeCl₃ in dichloroethane as solvent (0.05 M) at 23 °C for 16-24 h. ^aAddition of 5.0 equiv. of allyltrimethylsilane.

resulted in the formation of metathesis product **12** in 74% yield, the corresponding styrenyl analogs **11b-11f** initially showed little or no reactivity under identical reaction conditions. Subsequent studies revealed that the lack of reactivity can be attributed to competing product inhibition of the aryl aldehyde byproduct formed (see Supporting Information for details). Therefore, we focused on the evaluation of reagents capable of sequestering the corresponding aldehyde byproducts to avoid catalyst inhibition.^{5f} Ultimately, allyltrimethylsilane was iden-

tified as the most promising additive enabling catalytic carbonyl-olefin metathesis of electronically differentiated styrene derivatives in up to 78% yield (Table 2).

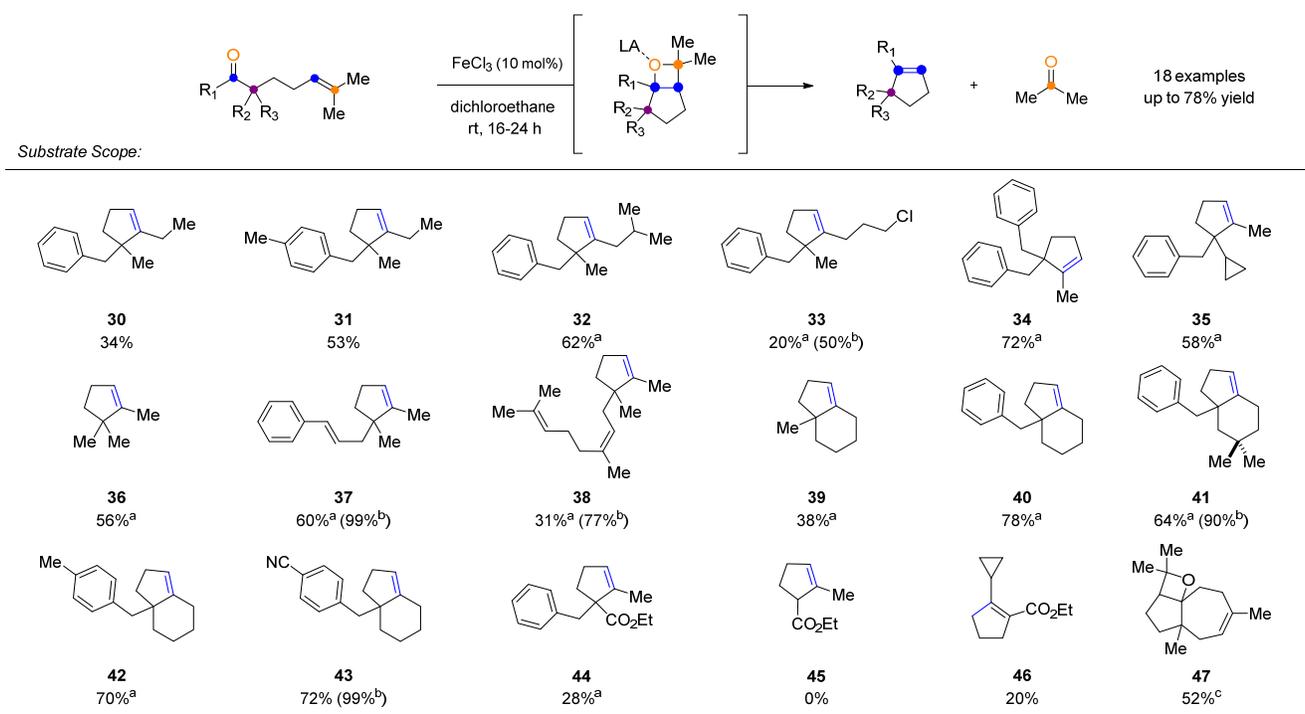
The optimized reaction conditions developed for the catalytic carbonyl-olefin metathesis of aliphatic ketones proved efficient for a variety of substrates incorporating distinct substituents and functional groups (Tables 3 and 4). Substrates including electron-deficient aryl residues in the β -position resulted in good to excellent yields of 63-93% of the desired metathesis products (**13-17**, Table 3). Electron-rich aryl-moieties bearing methyl, isopropyl, tert-butyl or methoxy substituents provided up to 94% yield of the desired products (**18-21**, Table 3). Additionally, substrates with methyl or chloro substituents in the ortho-position led to diminished yields of 63% and 50%, respectively (**25** and **26**), while meta-substituted substrates provided good yields ranging from 64-76% (**22-24**, Table 3). Interestingly, a thiophene-containing substrate was well tolerated under the reaction conditions resulting in 54% yield of the desired product **27**. In addition to methyl ketones, distinct aliphatic substituents including ethyl and isobutyl carbonyls were tolerated under the optimized reactions conditions (**30**, **31** and **32**, Table 4) although in slightly lower yields of 34-62%, presumably due to the increased steric bulk near the reactive carbonyl. Substrates bearing additional alkene functionalities, such as cinnamyl and geranyl substituents, proved compatible and resulted in the corresponding products **37** and **38** in 60% and 31% yield, respectively. Various substituents in the α -position to the carbonyl were tolerated under the reaction conditions. Cyclopentene **36** bearing two aliphatic moieties was obtained in 56% yield while cyclopropyl derivative **35** was formed in 58% isolated yield. Substrates bearing the β -ketoester moiety (**44**, **45**, and **46**, Table 4) yielded lower amounts of the metathesis products or did not undergo metathesis at all. Cyclohexyl carbonyl derivatives were efficient under the optimized reaction conditions leading to the formation of the corresponding bicyclic scaffolds in up to 78%

Table 3. Substrate scope of aryl variation.

Substrate Scope:

12 74% (99% ^b)	13 63% (94% ^b)	14 75% (99% ^b)	15 72% ^a	16 93% ^a (99% ^b)	17 84% ^a
18 94% ^a (97% ^b)	19 85% ^a (98% ^b)	20 68% ^a	21 38% (93% ^b)	22 73% (94% ^b)	23 72%
24 64% (83% ^b)	25 63% ^a (99% ^b)	26 50% (99% ^b)	27 54% ^a (96% ^b)	28 30% (50% ^b)	29 16% ^a

Conditions: All reactions were performed using 10 mol % of Lewis acid, FeCl₃, in DCE (0.05M) at 23 °C for 16-24 h or 80 °C for 3 h. ^bYields are based on recovered starting material. ^a50 mol % FeCl₃ in DCE (0.05M) at 0 °C to 23 °C.

Table 4. Substrate scope of distinct functional group incorporation.

Conditions: All reactions were performed using 10 mol % of Lewis acid, FeCl₃, in DCE (0.05M) at 23 °C for 16-24 h or 80 °C for 3 h. ^bYields are based on recovered starting material. ^c50 mol % FeCl₃ in DCE (0.05M) at 0 °C to 23 °C.

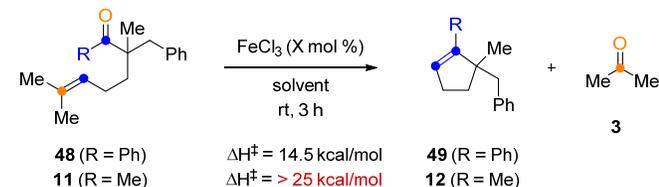
yield (**39-43**). Interestingly, a cycloheptyl-derived substrate did not result in the formation of the desired metathesis product, but led to the isolation of oxetane **47**¹¹ in 52% yield, providing additional support for the reaction mechanism.

Mechanistic Investigations

Over the course of our studies towards optimizing catalytic carbonyl-olefin metathesis reactions of aliphatic ketones, we note three key differences in reactivity compared to aryl ketone substrates. 1) FeCl₃-catalyzed carbonyl-olefin metathesis of aliphatic ketones proceeded best in dichloroethane as solvent re-

Table 5. Evaluation of solvent and catalyst loading for aryl (**48**) vs. aliphatic (**11**) ketone substrates.

A. Disparities in FeCl₃-Catalyzed COM of Aryl and Alkyl Ketones.



entry	R	FeCl ₃ (X mol %)	solvent	yield 49 or 12 (%)
1	Ph	5	toluene	65
2	Ph	5	dichloromethane	78
3	Ph	5	dichloroethane	99
4	Me	10	toluene	0
5	Me	10	dichloromethane	37
6	Me	10	dichloroethane	74

Conditions: All reactions were performed using 0.16 mmol of ketone **48** or **11** and Lewis acid in solvent (0.05 M) at 23 °C.

sulting in optimal yields of 74% (entry 6, Table 5). No product was observed relying on toluene as solvent and diminished yields of 37% under otherwise identical conditions were obtained in dichloromethane (entries 4 and 5, Table 5). In comparison, product formation in high yields ranging from 65% to 99% is observed when the corresponding aryl ketone **48** is reacted with 5 mol % of FeCl₃ in these solvents. 2) Higher catalyst loadings of 10 mol % FeCl₃ were shown to result in higher yields of the desired carbonyl-olefin metathesis product **12** while the analogous transformation of aryl ketones **48** proceeds in high yields with as little as 1 mol % FeCl₃. 3) Additionally, subsequent gas-phase simulations of the reaction path for FeCl₃-catalyzed carbonyl-olefin metathesis of aliphatic ketone **11** revealed activation barriers of >25 kcal/mol which are too high for the reaction to proceed. Comparatively, the corresponding activation barrier for aryl ketones was found to be 14.5 kcal/mol (Table 5).

Intrigued by the high reactivity of FeCl₃ and unique solvent dependence observed in the carbonyl-olefin metathesis of aliphatic ketone **11**, we initiated kinetic studies to obtain further insight into the controlling features of this transformation (Fig. 3). Mechanistic investigations of the catalytic carbonyl-olefin metathesis reaction of aryl ketone **1** had previously revealed a zero order dependence on substrate concentration and first order dependence in FeCl₃.^{5c} This indicated that the catalyst resting state has monomeric FeCl₃ bound to the substrate in Lewis acid-base complex **50** and undergoes a classic activation mode with a single Lewis acid monomer (Fig. 3). Similarly, carbonyl-olefin metathesis of aryl ketone **48** bearing an α -quaternary center was also found to have first order dependence on FeCl₃ concentration and zero order in substrate. Importantly, kinetic evaluation of the analogous aliphatic ketone **11** also displayed zero

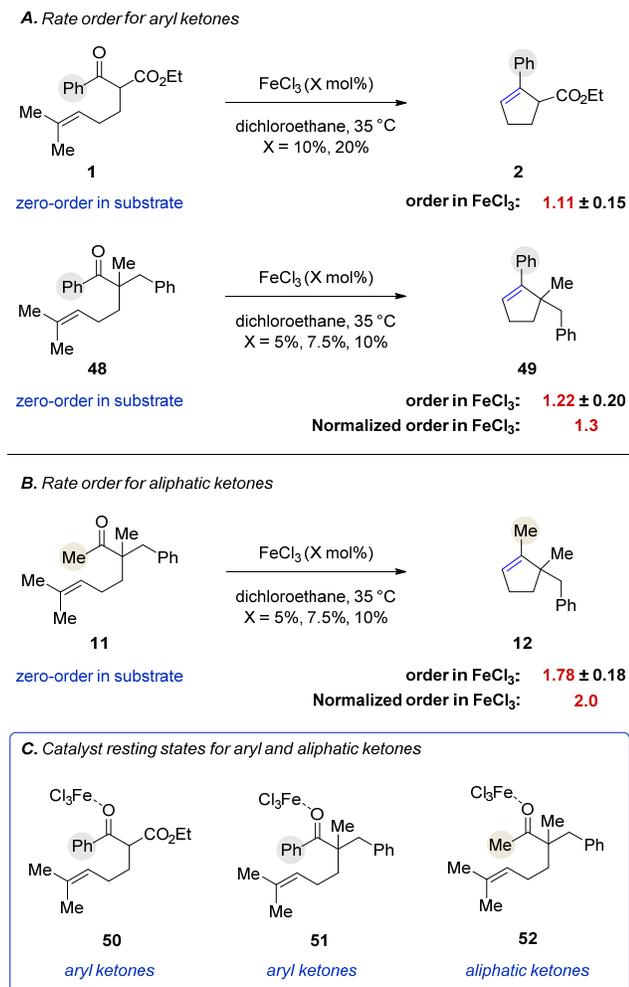
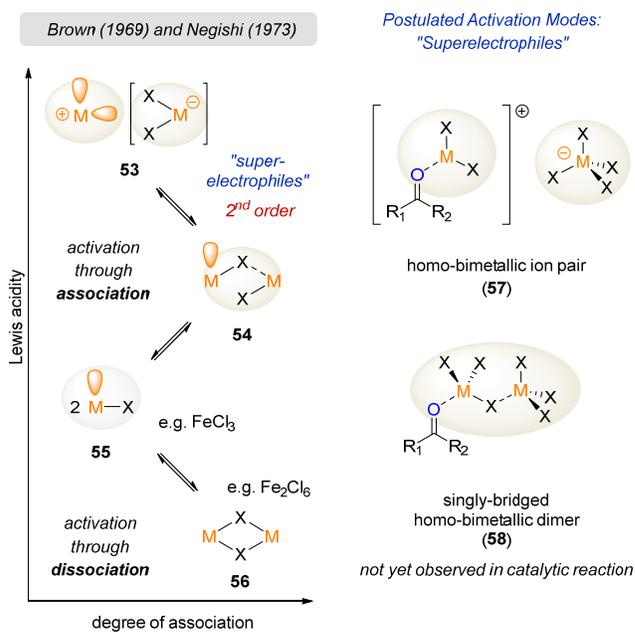
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Figure 3. Kinetic investigations of the catalytic carbonyl-olefin metathesis reaction with two independent methods relying on “initial rates” based on the decay of substrate and the “Normalized time scale method”. **A.** Rate order results for aryl ketones. **B.** Rate order results for aliphatic ketones. **C.** Catalytic resting states following kinetic investigation.

order with respect to substrate, which is consistent with a catalyst resting state of monomeric FeCl_3 bound to substrate (**52**, Fig. 3). However, ketone **11** was shown to proceed with second order kinetics in FeCl_3 ,^{12,13} implying that a different mode of Lewis acid activation is operative for aliphatic ketones (Fig. 3). Specifically, these kinetic results are consistent with a hypothesis that two equivalents of FeCl_3 are involved in the rate-determining step of carbonyl-olefin metathesis of aliphatic ketones while only one equivalent of FeCl_3 is involved in the analogous reaction of aryl ketones.

It has previously been postulated that individual Lewis acid monomers **55** could associate to form singly-bridged dimers **54** that retain an open coordination site rendering them as stronger Lewis acids than their corresponding monomers (Fig. 4A). This strategy was described as a “highly desirable”¹⁴ reaction design principle in Lewis acid catalysis as early as the 1960s as an approach to generate stronger Lewis acids by taking advantage of their inherent tendency to associate into “superelectrophiles”. Polarization of singly-bridged dimers **54** could induce subsequent ionization into doubly electron-deficient ion pairs **53**. Importantly, both singly-bridged dimers **54** and ion pairs **53** fall

A. Stronger Lewis Acids via Homobimetallic Association “Superelectrophiles”



B. Stoichiometric Homobimetallic Association of Lewis Acids

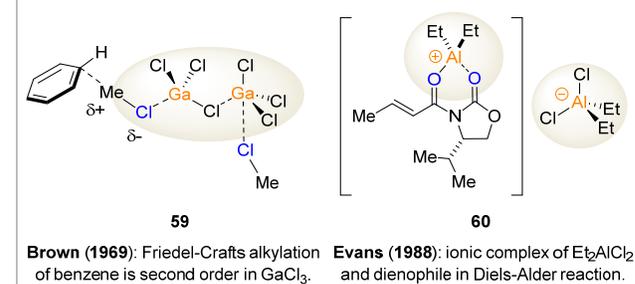


Figure 4. A. Lewis acid activation modes (M = metal) and postulated activation mode: “superelectrophiles”. B. Homobimetallic association of Lewis acids in Friedel-Crafts alkylation and Diels-Alder reactions.

under Olah’s definition of superelectrophiles¹⁵ by exhibiting reactivity that substantially exceeds that of their corresponding monomer **55**. While the synthetic realization and application of heterobimetallic superelectrophiles that result from the association of Lewis acids comprised of two different metals has led to important developments in organometallic chemistry,¹⁶ the related homobimetallic case is still considered uncommon.¹⁷ Consequently, the principle of homobimetallic association of Lewis acids has remained unexplored in catalysis. Isolated reports of

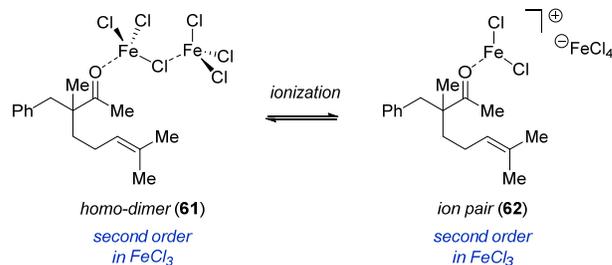
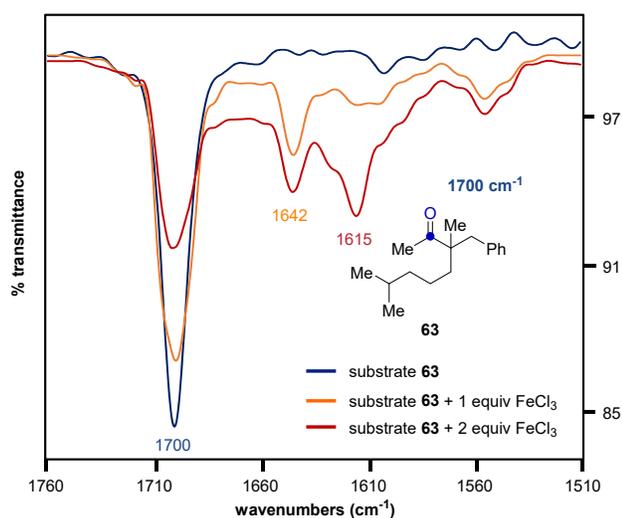
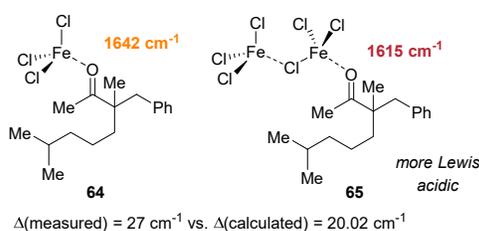


Figure 5. Proposed superelectrophiles for aliphatic ketones in catalytic carbonyl-olefin metathesis reactions.

A. IR Spectroscopic Measurements Support Iron-Dimer



B. Calculations Support IR Results



C. Raman Spectroscopic Measurements Support Iron-Dimer

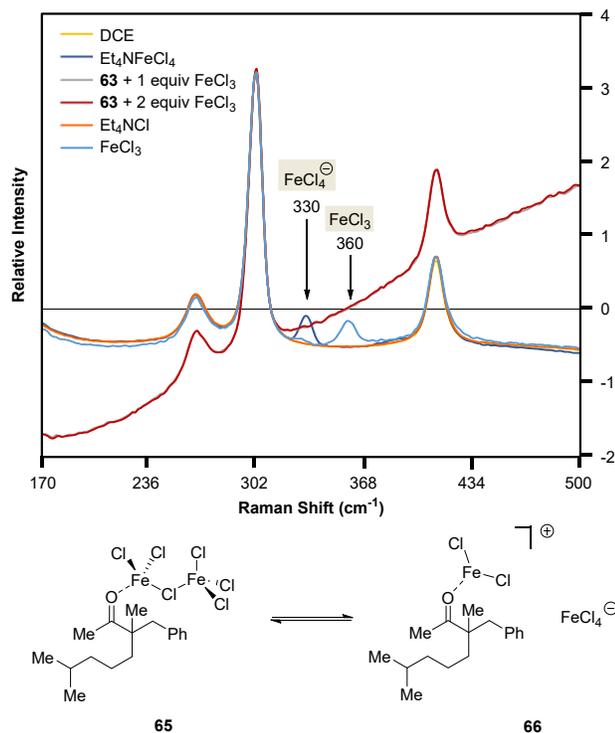


Figure 6. A. Infrared spectroscopic measurements of **63**. B. Calculations for IR data. C. Raman spectroscopic data of **63**.

homobimetallic association of Lewis acids have been postulated to be operative but exclusively in stoichiometric reaction settings. The observation of second order rate dependence in GaCl_3 -mediated Friedel-Crafts alkylations¹⁸ led Brown and

coworkers to suggest an activation mode based on Lewis acid superelectrophiles (**59**, Fig. 4B) but dimers **54** or ion pairs **53** could not be differentiated. Later, Evans suggested carbonyl activation by homobimetallic ion pairs **60** in stoichiometric Et_2AlCl -mediated Diels-Alder reactions to account for unique reactivity observed with Al-based Lewis acids (Fig. 4B).^{19,20,21}

Based on this literature precedent and our results obtained in the kinetic investigations, we considered two distinct activation modes for aliphatic ketones in catalytic carbonyl-olefin metathesis reactions relying on singly-bridged FeCl_3 dimer (**61**) or ion pair (**62**) (Fig. 5). In the neutral pathway, the first equivalent of FeCl_3 binds aliphatic ketone **11** to form the catalyst resting state **52**. Coordination of a second equivalent of FeCl_3 generates singly-bridged homobimetallic dimer **61** (Fig. 5) as a Lewis acid superelectrophile. The resulting increase in substrate polarization leads to efficient activation of the substrate for carbonyl-olefin metathesis. Alternatively, homobimetallic dimer **61** can undergo solvent-assisted polarization to result in ion pair **62**, which similarly represents a Lewis acid superelectrophile capable of activating the substrate for carbonyl-olefin metathesis.

In order to gain initial support for the formation of Lewis acid superelectrophiles and differentiate between neutral singly-bridged dimers or ion pairs as active catalytic species, we conducted infrared spectroscopic measurements that relate Lewis acid-carbonyl activation to Lewis acid strength based on the change in absorption frequency observed.^{22,23} A new signal with an absorption frequency of 1642 cm^{-1} is observed when ketone **63** is treated with equimolar amounts of FeCl_3 , consistent with

EPR Spectroscopic Measurements Support Catalyst Resting State

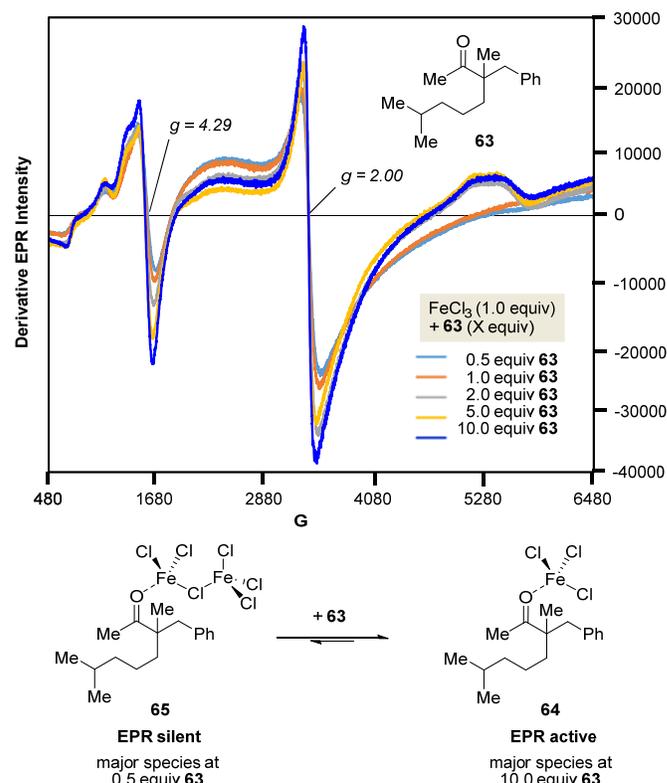
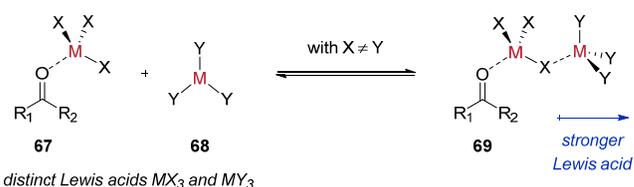


Figure 7. Electron paramagnetic resonance spectroscopic measurements of **63**.

single carbonyl activation upon coordination of FeCl_3 to form complex **64** (Fig. 6A). Addition of a second equivalent of FeCl_3 resulted in a third signal with a lower absorption frequency at 1615 cm^{-1} , suggesting increased carbonyl activation of **63** by a stronger Lewis acid. Both the singly-bridged FeCl_3 dimer (**61**) and the corresponding ion pair (**62**) are expected to lower carbonyl absorption frequencies upon coordination and are consistent with calculations of the expected differences in shifts of absorption frequencies that match the experimentally observed shifts ($\Delta C=O_{\text{measured}}$ vs. $\Delta C=O_{\text{calc.}}$: 27 vs. 20.0 cm^{-1}) (Fig. 6B).

Experiments relying on Raman spectroscopy show no formation of FeCl_4^- (330 cm^{-1})^{25,26} upon addition of FeCl_3 to aliphatic ketone **63** in dichloroethane (Fig. 6C) indicating that the ion pair **66** is not present. Electron paramagnetic resonance (EPR) experiments were performed to gain further support for the catalyst resting state in this transformation and distinguish between singly-bridged dimers or ion pairs as active catalytic species. Increasing amounts of aliphatic ketone **63** were added to a solution of FeCl_3 in dichloroethane while the concentration of FeCl_3 remained the same (Fig. 7). High spin EPR spectra with $g = 4.29$ were obtained for all ratios of **63** bound to FeCl_3 as expected for iron (III) species. The addition of excess aliphatic ketone **63** leads to an increase in signal strength, consistent with an iron(III)-bound complex **64** as the major species in solution and supports the catalyst resting state of monomeric FeCl_3 bound to substrate. In comparison, the singly-bridged

A. Hypothesis: Fe(III)-Salts with Distinct Halide Ligands Form Stronger Acids



B. Application to Carbonyl-Olefin Metathesis of Aliphatic Ketones

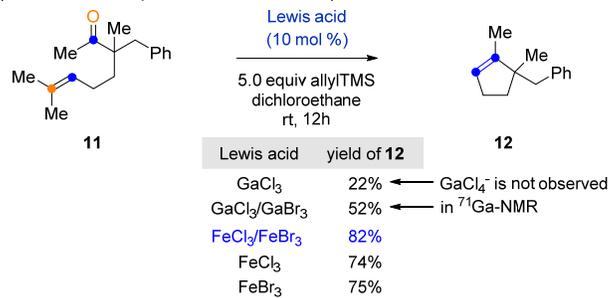
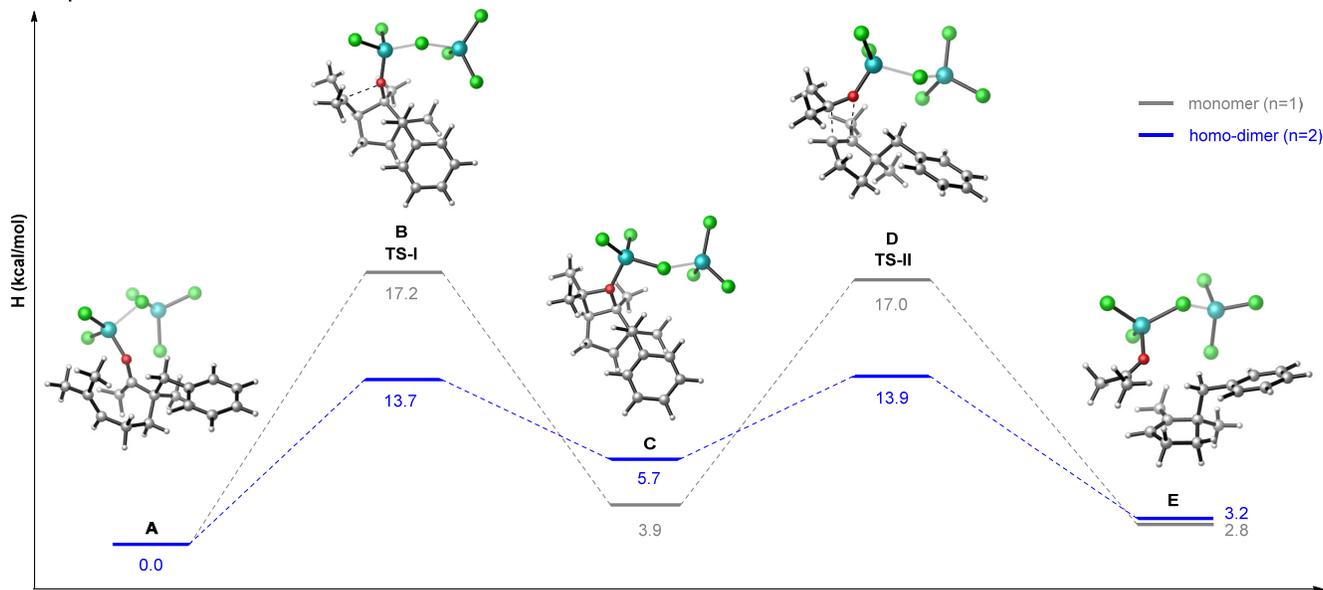


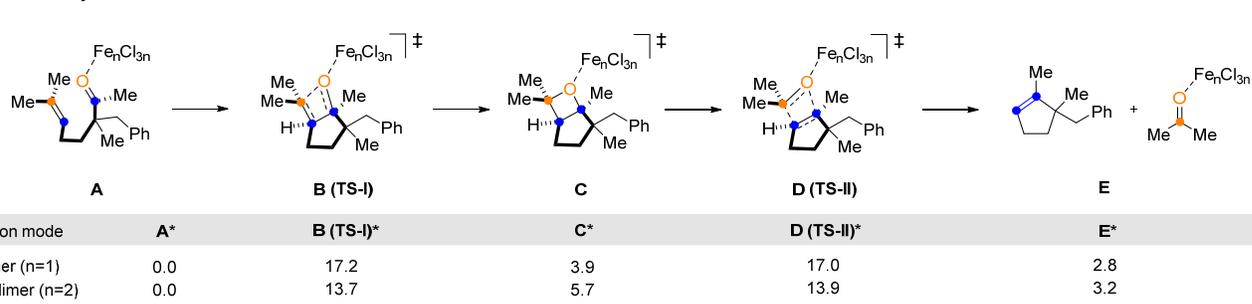
Figure 8. A. Proposed homobimetallic super Lewis acid utilizing different Lewis acids. **B.** Generation of stronger super Lewis acids with MCl_3 and MBr_3 to increase reactivity.

homo-dimer **65** is expected to be favored with an excess of FeCl_3 relative to ketone **63**. While the homo-dimer **65** is EPR silent, the corresponding monomeric complex **64** is EPR active

A. Enthalpic Profile:



B. Reaction Pathway:



*values refer to enthalpies H in kcal/mol

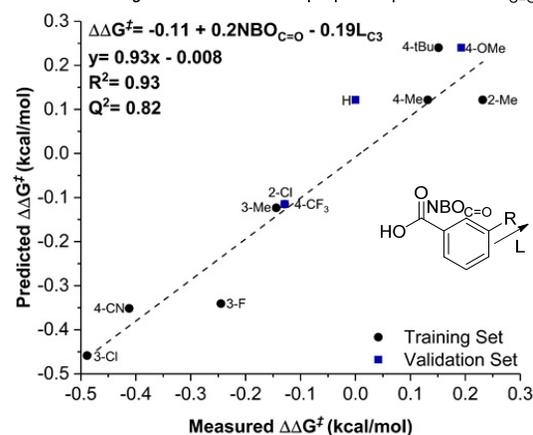
Figure 9. Quantum chemical investigations. A. Enthalpic profile and **B.** reaction pathway of the computationally proposed reaction mechanism for carbonyl-olefin metathesis of aliphatic ketones using FeCl_3 .

in accordance with the observed signal. Importantly, no signal is observed for the FeCl_4^- anion, which is EPR-active,²⁴ providing additional support for a neutral reaction pathway.

These combined mechanistic investigations and substrate evaluation in the carbonyl-olefin metathesis reaction of aliphatic ketones support a carbonyl-activation mode based on iron(III) homo-dimers as superelectrophiles. To reinforce this hypothesis, we examined the possibility of generating even more reactive dimers functioning as Lewis acidic superelectrophiles which could lead to increased yields of the desired metathesis products. The composition of GaCl_3 and GaBr_3 mixtures in non-polar solvents has previously been studied by Černý and coworkers.²⁷ Specifically, halogen exchange between both Lewis acids was shown to occur and the predominant species at equimolar composition are $\text{Ga}_2\text{Cl}_3\text{Br}_3$ and $\text{Ga}_2\text{Cl}_4\text{Br}_2$. We postulated that two distinct iron-derived Lewis acids bearing substituents differing in electronegativity, specifically FeCl_3 and FeBr_3 , would also undergo halogen exchange in solution to form a stronger Lewis acidic superelectrophile *in situ* which could result in increased yields of the desired metathesis product (Fig. 8). When 10 mol % of a 1:1 ratio of FeCl_3 and FeBr_3 was used with ketone **11**, the desired carbonyl-olefin metathesis product was obtained in a slightly higher yield when compared to the FeCl_3 homo-dimer (82% yield vs. 74% yield). This result is consistent with the hypothesis that stronger superelectrophiles can be generated from dissimilar iron-based Lewis acids and result in increased substrate activation (see Supporting Information for additional experimental and spectroscopic details on this experiment).

As a next step, quantum chemical simulations were performed to probe the mechanism of catalytic carbonyl-olefin metathesis reaction of aliphatic ketones.^{28,29} These simulations were performed using density functional theory at the B97-D level including implicit solvation, see Supporting Information for more details. Figure 9 shows the most favorable reaction pathway found for the monomeric FeCl_3 -substrate complex (shown in grey) and the corresponding singly-bridged homo-dimer (shown in blue). Both pathways consist of concerted, asynchronous ring-closing (B) and ring-opening (D) steps involving an oxetane intermediate C, which were operative in the carbonyl-olefin metathesis of aryl ketones. The overall barriers, however, show that the initial step of the reaction is enthalpically preferred by 3.5 kcal/mol when two equivalents of FeCl_3 are bound to the substrate in a homo-dimeric manner. The most favored computed metathesis pathway is the Lewis acid activation of a Lewis acid, which ultimately leads to a superelectrophile functioning as a stronger catalyst consistent with contraction of the Fe-O bond by 0.05 Å in A compared to the monomeric FeCl_3 -complex (see Supporting Information for details). Likewise, the Fe-Cl distance of the Fe-Cl-Fe bridge is elongated by 0.12 Å, resulting in charge transfer from the first iron to the second iron as this bond is activated. In total, a single FeCl_3 molecule is able to withdraw 0.33 electrons from the substrate, but two molecules of FeCl_3 extract 0.45 units of charge. This increased charge withdrawal through this singly-bridged dimer is needed for aliphatic substrates, but seemingly not for the corresponding aryl analogs due to the ability of aryl ketones to delocalize charge through conjugation. These simulations are therefore consistent with spectroscopic results, which display increased

A. MLR model using benzoic acids as simple probes prioritizes $\text{NBO}_{\text{C}=\text{O}}$.



B. Univariate correlation between $\text{NBO}_{\text{C}=\text{O}}$ and measured $\Delta\Delta G^\ddagger$.

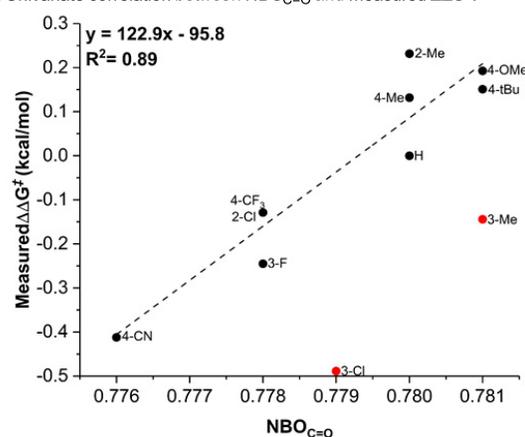


Figure 10. Evaluation of aromatic α -substituent features dictating rate in the reaction of aliphatic ketones. **A.** MLR model using benzoic acids as simple probes prioritizes $\text{NBO}_{\text{C}=\text{O}}$ and sterimol L as key contributing factors in the benzylic series. **B.** Univariate correlation between $\text{NBO}_{\text{C}=\text{O}}$ and measured $\Delta\Delta G^\ddagger$. Red points represent outliers with large substituents at the 3-position that perform worse than expected based on electron density effects alone.

carbonyl activation when multiple units of Lewis acid are available and are also in accordance with the observed second order rate dependence of FeCl_3 .

While we have demonstrated the use of the carbonyl olefin metathesis reaction on a wide range of aliphatic substrates, the significant changes in structure coupled with the competitive binding scenarios to the Lewis acid make it difficult to separate the individual features of the substrate that impact the reaction outcome. To avoid the complexity of connecting the substrate structure to more than one fundamental process, we hypothesized that analysis of a modular model substrate class could offer more informative insight into the substrate sensitivities to a singular reaction event. The diversity of the benzylic-derived substrates (Table 3) offers the requisite changes to both the remote electronic and steric environments (Fig. 10) for a training set but also incorporates sufficient overlapping features for analysis. The relative rate values were measured for 12 substrates under uniform reaction conditions and, as expected, do not mirror the trend in the associated isolated yields, suggesting

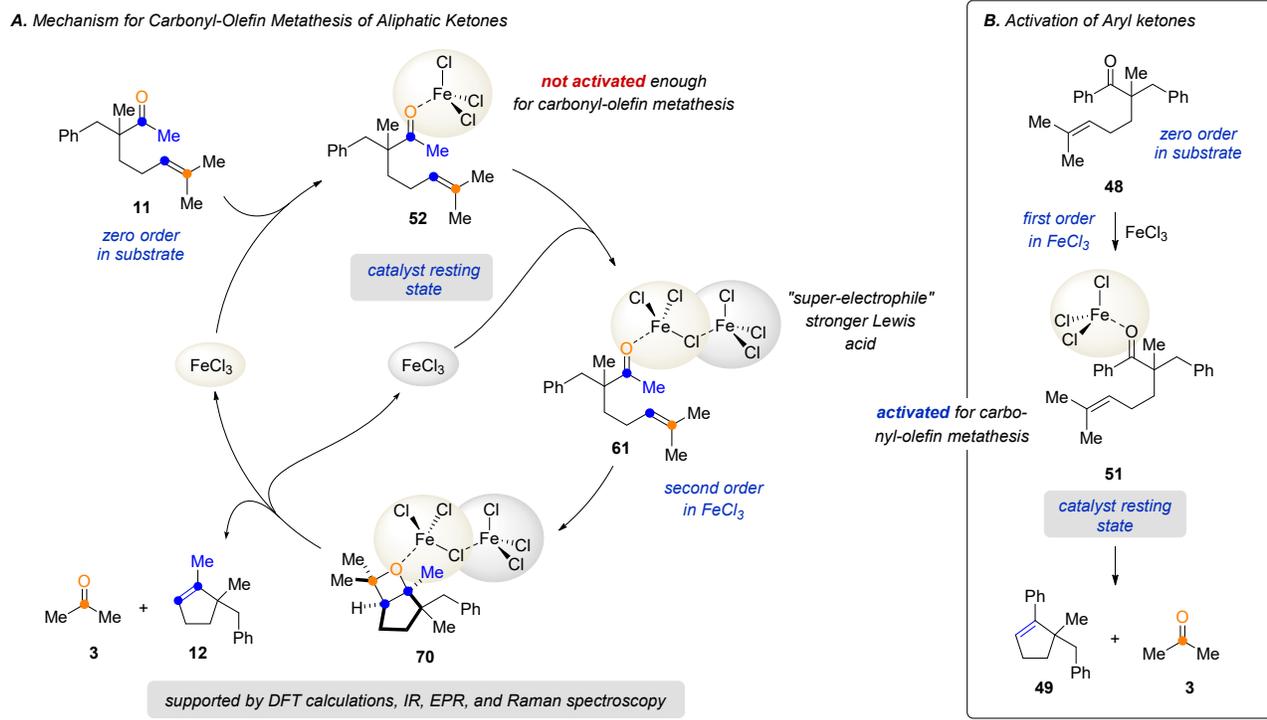


Figure 11. A. Mechanistic hypothesis presenting reactive activation mode for aliphatic ketones requiring second coordination of FeCl_3 to undergo metathesis. B. Substrate activation of aryl ketone substrates by monomeric FeCl_3 .^{5c}

other events contribute to this outcome. Considering the substituents under evaluation, we employed the corresponding benzoic acids on the basis of the Sigman group's recent effort to develop enhanced parameter sets using these simple surrogates.³⁰ Computation optimizations were performed at the M06-

2X/def2-TZVP level of theory wherein NBO charges, IR vibrations and Sterimol values were collected to probe structural effects.³¹ These parameters were correlated to $\Delta\Delta G^\ddagger$, calculated using the equation $\Delta\Delta G^\ddagger = -RT \ln(k_{\text{rel}})$, by using linear regression fitting to quantitatively analyze the substituent effects on reaction rate. A two parameter model was sufficient to describe the structural effects of this subset of substrates affecting the rate of reaction (Fig. 10A). Note that a reasonable linear correlation can only be obtained after the removal of the 4-Br substrate ($R^2 = 0.46$, if included). Electron density measured through the $\text{NBO}_{\text{C=O}}$ charge, was found to be the most significant reactivity discriminant, in which increasing the electron donating ability of the substituent on the aromatic ring increased the rate of reaction. Steric effects were of little consequence to rate and were only pronounced when substituents larger than fluorine were introduced at the 3-position, which slow the rate of reaction substantially. Reasonable steric bulk at the 3-position is not taken into account by $\text{NBO}_{\text{C=O}}$ therefore displaying two outliers (Fig. 10B). This data is in agreement with the hypothesis that a stronger Lewis acid initially accelerates the reaction rate to allow for the less reactive aliphatic substrates to undergo metathesis.

Based on these combined results, we propose separate activation modes for Lewis acid-catalyzed carbonyl-olefin metathesis reactions of aryl and aliphatic ketones. When considering aryl ketones, the catalyst resting state **51**, in which monomeric

FeCl_3 ^{32,33} is bound to substrate, is sufficiently activated to undergo carbonyl-olefin metathesis. This is consistent with the observed first order kinetics in FeCl_3 and our computational investigations which identified the aryl moiety as an essential structural component for transition state stabilization by delocalizing electron density to facilitate formation of the oxetane intermediate.^{5c} In comparison, aliphatic ketones are devoid of this stabilization and thus the catalyst remains in its resting state **52** until a second equivalent of FeCl_3 binds to form singly-bridged homo-dimer **61**. This homobimetallic association of a second equivalent of FeCl_3 generates a stronger Lewis acid which functions as a superelectrophile that is capable of lowering the energy of the transition state to provide sufficient activation for carbonyl-olefin metathesis (Fig. 11). The resulting increase in substrate polarization leads to formation of intermediate oxetane **70**, which upon subsequent fragmentation results in the desired metathesis product **12** and acetone byproduct **3**.

Studies by Wong and Brown^{33a} have shown that Lewis acids, such as GaCl_3 , are stabilized in hydrocarbon solvents. Specifically, $\text{GaCl}_3\text{-Cl-R}$ adducts are formed and the stability of these decreases with increased branching of the hydrocarbon solvents. Consequently, $\text{FeCl}_3\text{-DCE}$ adducts are expected to be less stable than $\text{FeCl}_3\text{-DCM}$ adducts which is consistent with DCE being the superior solvent in carbonyl-olefin metathesis reactions of aliphatic ketones. Additionally, DCE has a higher capability to stabilize charge due to its increased dielectric constant compared to DCM, which also aids the transition state stabilization of carbonyl-olefin metathesis reactions of aliphatic ketones (see Supporting Information for details).

Conclusion

Lewis acid activation through bimetallic association was postulated sixty years ago as a viable avenue to generate stronger Lewis acid catalysts. While this concept has been advanced in the context of heterobimetallic association, the corresponding homobimetallic association was considered to be “of little or no synthetic consequence”.¹⁷ The results presented herein show that the concept of Lewis acid activation by association can be expanded to include homobimetallic interactions as a desirable reactivity mode. We demonstrate the synthetic realization and importance that homobimetallic association has in Lewis acid catalysis by accessing superelectrophiles *in situ* to give rise to more potent catalytic species. These proposed superelectrophilic singly-bridged iron(III) homo-dimers lead to more reactive Lewis acid-complexes that are capable of activating previously unreactive substrates for the catalytic carbonyl-olefin metathesis reactions of aliphatic ketones.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI:

General methods; detailed experimental studies; computational experiments; ¹H and ¹³C NMR spectra

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ACKNOWLEDGMENT

This work was supported by the NIH/National Institute of General Medical Sciences (R01-GM118644 to C.S.S. and R35GM128830 to P.M.Z.), the National Science Foundation (CHE-1763436 to M.S.S.), the Alfred P. Sloan Foundation and the David and Lucile Packard Foundation (fellowships to C.S.S.). H.A., C.C.M. and J.R.L. thank the National Science Foundation for predoctoral fellowships (DGE 1256260). Computational resources were provided by the Center for High Performance Computing at the University of Utah and the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by the NSF (ACI-1548562). We are very grateful to Prof. Nathaniel Szymczak, Prof. Adam Matzger, Prof. Nicolai Lehnert, Andrew Hunt and Corey White (University of Michigan) for help conducting IR, Raman and EPR spectroscopic measurements as described in this manuscript and accompanying supporting information. Prof. James Devery (Loyola University Chicago) is gratefully acknowledged for helpful suggestions regarding the kinetic measurements described in this manuscript.

REFERENCES

- (1) For carbonyl-olefin metathesis reactions proceeding via oxetane photoadducts, see: (a) Jones, G., II; Schwartz, S.B.; Marton, M.T. *J. Chem. Soc., Chem. Commun.* **1973**, *11*, 374-375. (b) Jones, G., II; Acquadro, M.A.; Carmody, M.A. *J. Chem. Soc., Chem. Commun.* **1975**, *6*, 206-207. (c) Carless, H.A.J.; Trivedi, H.S. *J. Chem. Soc., Chem. Commun.* **1979**, *8*, 382-383. (d) D'Auria, M.; Racioppi, R.; Viggiani, L. *Photochem. Photobiol. Sci.* **2010**, *9*, 1134-1138. (e) Pérez-Ruiz, R.; Gil, S.; Miranda, M.A. *J. Org. Chem.* **2005**, *70*, 1376-1381. (f) Pérez-Ruiz, R.; Miranda, M.A.; Alle, R.; Meerholz, K.; Griesbeck, A.G. *Photochem. Photobiol. Sci.* **2006**, *5*, 51-55. (g) Valiulin, R.A.; Kutateladze, A.G. *Org. Lett.* **2009**, *11*, 3886-3889. (h) Valiulin, R.A.; Arisco, T.M.; Kutateladze, A.G. *J. Org. Chem.* **2011**, *76*, 1319-1332. (i) Valiulin, R.A.; Arisco, T.M.; Kutateladze, A.G. *J. Org. Chem.* **2013**, *78*, 2012-2025.
- (2) Fu, G.C.; Grubbs, R.H. *J. Am. Chem. Soc.* **1993**, *115*, 3800-3801.

- (3) For organocatalytic approaches, see: (a) Griffith, A.K.; Vanos, C.M.; Lambert, T.H. *J. Am. Chem. Soc.* **2012**, *134*, 18581-18584. (b) Hong, X.; Liang, Y.; Griffith, A.K.; Lambert, T.H.; Houk, K.N. *Chem. Sci.* **2014**, *5*, 471-475.
- (4) For Brønsted and Lewis acid mediated carbonyl-olefin metathesis reactions, see: (a) Schopov, I.; Jossifov, C. *Chem., Rapid Commun.* **1983**, *4*, 659-662. (b) Soicke, A.; Slavov, N.; Neudörfl, J.-M.; Schmalz, H.-G. *Synlett* **2011**, *17*, 2487-2490; (c) van Schaik, H.-P.; Vijn, R.-J.; Bickelhaupt, F. *Angew. Chem. Int. Ed.* **1994**, *33*, 1611-1612. (d) Jossifov, C.; Kalinova, R.; Demonceau, A. *Chim. Oggi* **2008**, *26*, 85-87.
- (5) (a) Ludwig, J.R.; Zimmerman, P.M.; Gianino, J.B.; Schindler, C.S. *Nature* **2016**, *533*, 374-379. (b) McAtee, C.M.; Riehl, P.S.; Schindler, C.S. *J. Am. Chem. Soc.* **2017**, *139*, 2960-2963. (c) Ludwig, J.R.; Phan, S.; McAtee, C.M.; Zimmerman, P.M.; Devery III, J.J.; Schindler, C.S. *J. Am. Chem. Soc.* **2017**, *139*, 10832-10842. (d) Groso, E.J.; Golonka, A.N.; Harding, R.A.; Alexander, B.W.; Sodano, T.M.; Schindler, C.S. *ACS Catalysis* **2018**, *8*, 2006-2011. (e) Albright, H.; Vonesh, H.L.; Becker, M.R.; Alexander, B.W.; Ludwig, J.R.; Wiscons, R.A.; Schindler, C.S. *Org. Lett.* **2018**, *20*, 4954-4958. (f) Ma, L.; Li, W.; Xi, H.; Bai, X.; Ma, E.; Yan, X.; Li, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 10410-10413. (g) For example, a single literature report of an aluminum-mediated fragmentation of aliphatic oxetanes exists resulting in 30% yield of the corresponding olefin product: Jackson, A.C.; Goldman, B.E.; Snider, B.B. Intramolecular and intermolecular Lewis acid catalyzed ene reactions using ketones as enophiles. *J. Org. Chem.* **1984**, *49*, 3988-3994. In comparison, boron trifluoride and Brønsted acid-mediated fragmentation of oxetanes bearing aromatic moieties are more prominent. For an example, see: Carless, H.A.J., Trivedi, H.S. *J. Chem. Soc. Chem. Comm.* **1979**, *8*, 382-383.
- (6) For a review on Lewis acid-catalyzed carbonyl-olefin metathesis reactions, see: Ludwig, J.R.; Schindler, C.S. *Synlett* **2017**, *28*, 1501-1509.
- (7) For approaches relying on carbocation-based Lewis acids as catalysts in carbonyl-olefin metathesis, see: (a) Bah, J.; Franzén, J.; *Eur. J. Org. Chem.* **2015**, *8*, 1834-1839; (b) Tran, U.P.N.; Oss, G.; Pace, D.P.; Ho, J.; Nguyen, T.V. *Chem. Sci.* **2018**, *9*, 5145-5151.
- (8) For an approach relying on Brønsted acid-catalyzed carbonyl-olefin metathesis reactions inside a supramolecular host, see: (a) Catti, L.; Tiefenbacher, K. *Angew. Chem. Int. Ed.* **2018**, *57*, 14589-14592. For an iodine-catalyzed approach, see: (b) Nguyen, T.V., Tran, U.P.N., Oss, G., Breugst, M., Detmar, E., Liyanto, K. *ChemRxiv*. doi:10.26434/chemrxiv.7057913.
- (9) Ludwig, J.R., Watson, R.B., Nasrallah, D.J., Gianino, J.B., Zimmerman, P.M., Wiscons, R., Schindler, C.S. *Science*, **2018**, *361*, 1363-1369.
- (10) Unpublished results.
- (11) Demole, E., Enggist, P., Borer, M.C. *Helv. Chim. Acta.* **1971**, *54*, 1845-1864.
- (12) Baxter, R.D., Sale, D., Engle, K.M., Yu, J., Blackmond, D.G. *J. Am. Chem. Soc.* **2012**, *134*, 4600-4606.
- (13) Burés, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 2028-2031.
- (14) Negishi, E. *Chem. Eur. J.* **1999**, *5*, 411-420.
- (15) (a) Olah, G.A. *Angew. Chem. Int. Ed.* **1993**, *32*, 767-788. (b) Olah, G.A., Klumpp, D.A. *Superelectrophiles and Their Chemistry*. Wiley-VCH Verlag GmbH & Co. KGaA 2007.
- (5) Shambayati, S., Crowe, W.E., Schreiber, S.L. *Angew. Chem. Int. Ed.* **1990**, *29*, 256-272.
- (16) In comparison, the corresponding heterobimetallic association of two different metal-derived Lewis acids have been widely investigated to induce distinct reactivity, such as ate complexation and transmetalation. For examples, see: (a) Sugawara, T., Toyoda, T., Adachi, M., Sasakura, K. *J. Am. Chem. Soc.* **1978**, *100*, 4842-4852. (b) Douglas, A.W., Abramson, N.L., Houpis, I.N., Karady, S., Molina, A., Xavier, L.C., Yasuda, N. *Tetrahedron Lett.* **1994**, *35*, 6807-6810.
- (17) Negishi, E. *Pure & Appl. Chem.* **1981**, *53*, 2333-2356.
- (18) DeHaan, F.P., Brown, H.C. *J. Am. Chem. Soc.* **1969**, *91*, 4844-4850.
- (19) Evans, D.A., Chapman, K.T., Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.

- 1 (20) Castellino, S., Dwight, W.J. *J. Am. Chem. Soc.* **1993**, *115*, 2986-
2 2987.
- 3 (21) Lam, Y.-h., Cheong, P. H.-Y., Blasco Mata, J.M., Stanway, S. J.,
4 Gouverneur, V., Houk, K.N. *J. Am. Chem. Soc.* **2009**, *131*, 1947-1957.
- 5 (22) Cook, D. *Can. J. Chem.* **1963**, *41*, 522-526.
- 6 (23) Hilt, G., Pünner, F., Möbus, J., Naseri, V., Bohn, M.A. *Eur. J. Org.*
7 *Chem.* **2011**, 5962-5966.
- 8 (24) Hertel, G.R., Clark, H.B. *J. Phys. Chem.* **1961**, *65*, 1930-1932.
- 9 (25) Sitze, M.S., Schreiter, E.R., Patterson, E.V., Freeman, R.G. *Inorg.*
10 *Chem.* **2001**, *40*, 2298-2304.
- 11 (26) Wyrzykowski, D., Maniecki, T., Pattek-Janczyk, A., Stanek, J.,
12 Warnke, Z. *Thermochimica Acta* **2005**, *435*, 92-98.
- 13 (27) Cerny, Z., Machacek, J., Fusek, J., Casensky, B., Kriz, O., Tuck,
14 D.G. *J. Organometallic Chem.* **1993**, *465*, 25-30.
- 15 (28) Zimmerman, P.M. *J. Comput. Chem.* **2015**, *36*, 601-611.
- 16 (29) Pendleton, I.M.; Pérez-Temprano, M.H.; Sanford, M.S.; Zimmer-
17 man, P.M. *J. Am. Chem. Soc.* **2016**, *138*, 6049-6060.
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
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- 31
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- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60
- (30) Santiago, C.B., Milo, A., Sigman, M.S. *J. Am. Chem. Soc.* **2016**,
138, 13424-13430.
- (31) For reviews on this approach, see: (a) Santiago, C. B., Guo, J.-Y.,
Sigman, M.S. *Chem. Sci.* **2018**, *9*, 2398-2412. (b) Sigman, M. S., Har-
per, K. C., Bess, E. N., Milo, A. *Acc. Chem. Res.*, **2016**, *49*, 1292-
1301.
- (32) Asakura, K., Nomura, M., Kuroda, H. *Bull. Chem. Soc. Jpn.* **1985**,
58, 1543-1550.
- (33) Interactions of GaCl₃ with chlorinated solvents are well investi-
gated and suggest that GaCl₃ is monomeric in chlorinated hydrocar-
bons. For details, see (a) Wong, R., Brown, H.C. *J. Inorganic and Nu-
clear Chemistry* 1955, *1*, 402-410. (b) DeHaan, F.P., Brown, H.C. *J.*
Am. Chem. Soc. 1969, *91*, 4844-4850. (c) DeHaan, F.P.; Gibby, M.G.;
Aebersold, D.R. *J. Am. Chem. Soc.* 1969, *91*, 4860-4863.

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