Carbonyl-Olefin Metathesis

2019.04.13

Yinghua Wang

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1. Introduction of carbonyl-olefin metathesis

2. Fe(III)-catalyzed carbonyl-olefin metathesis of aryl ketone (Schindler, 2016)

LETTER

doi:10.1038/nature17432

Iron(III)-catalysed carbonyl–olefin metathesis

Jacob R. Ludwig[1], Paul M. Zimmerman[1], Joseph B. Gianino[1] & Corinna S. Schindler[1]

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Article

Cite This: *J. Am. Chem. Soc.* 2019, 141, 1690–1700

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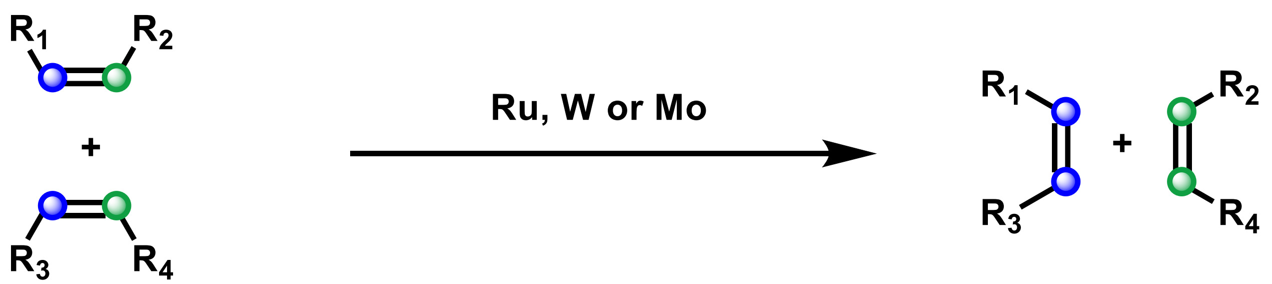
Catalytic Carbonyl-Olefin Metathesis of Aliphatic Ketones: Iron(III) Homo-Dimers as Lewis Acidic Superelectrophiles

Haley Albright,[†] Paul S. Riehl,[†] Christopher C. McAtee,[†] Jolene P. Reid,[§] Jacob R. Ludwig,[†] Lindsey A. Karp,[†] Paul M. Zimmerman,[†] Matthew S. Sigman,[§] and Corinna S. Schindler*,[†]

Introduction of Metathesis

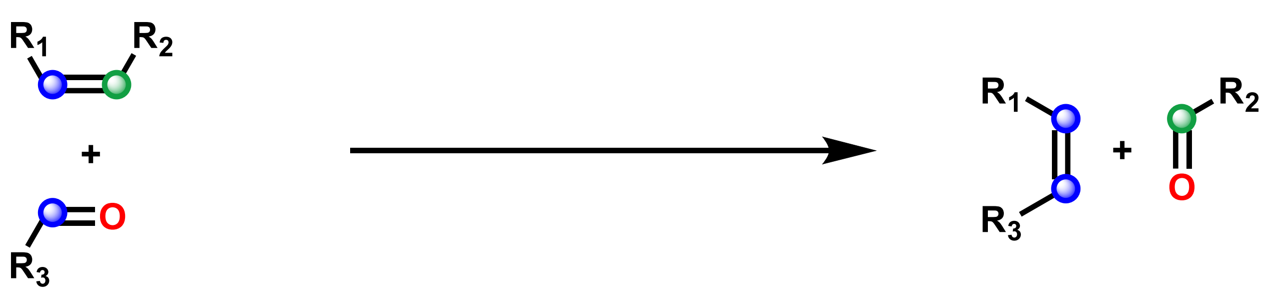
Metathesis: Exchange of substituents between different olefins

Olefin-olefin metathesis



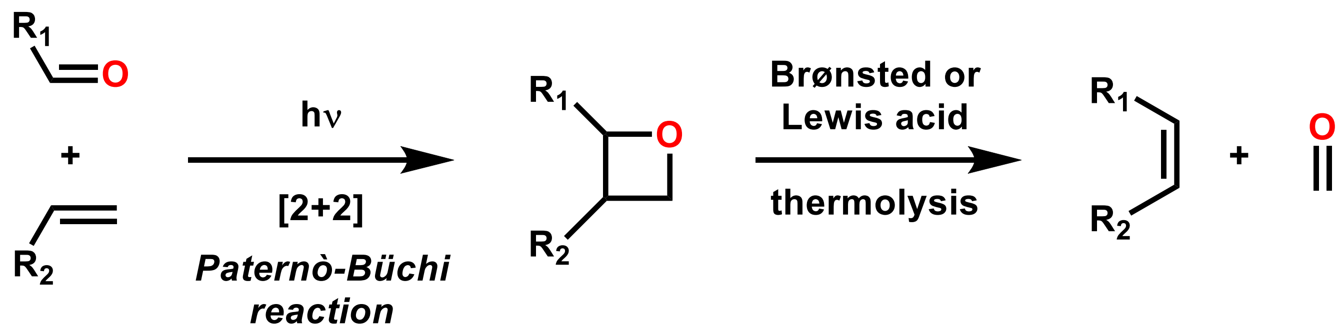
One of the most powerful carbon-carbon bond-forming reactions

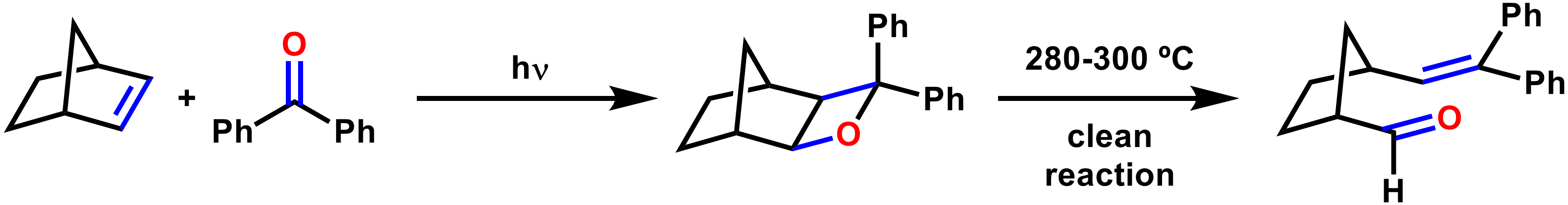
Carbonyl-olefin metathesis

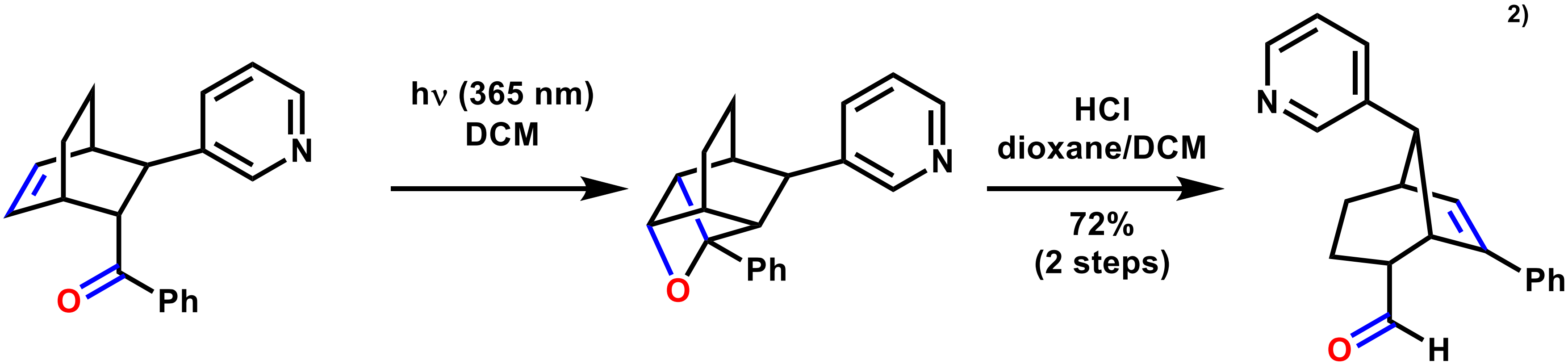


Much less developed than olefin-olefin metathesis

Photochemical Carbonyl-Olefin Metathesis

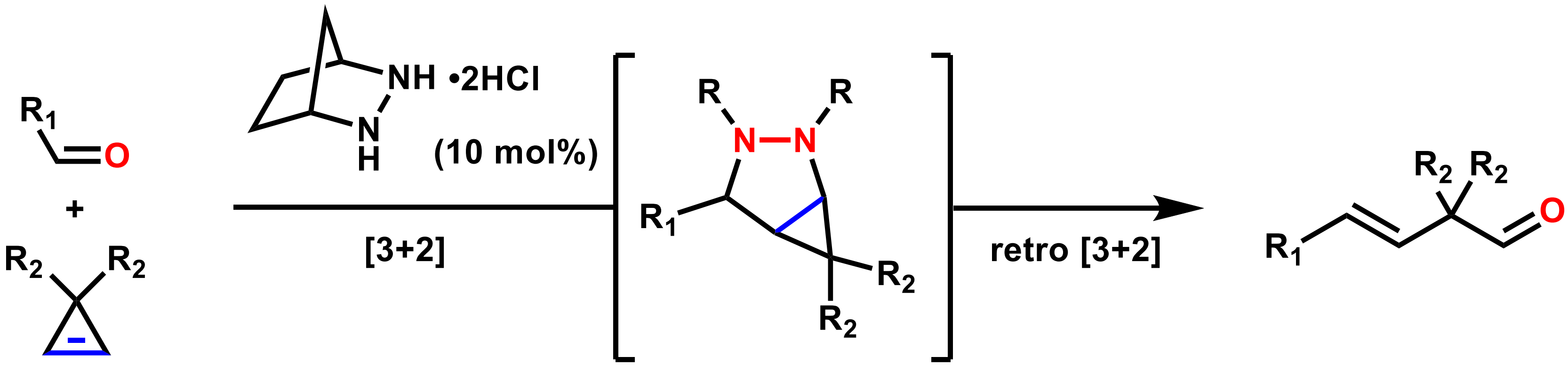


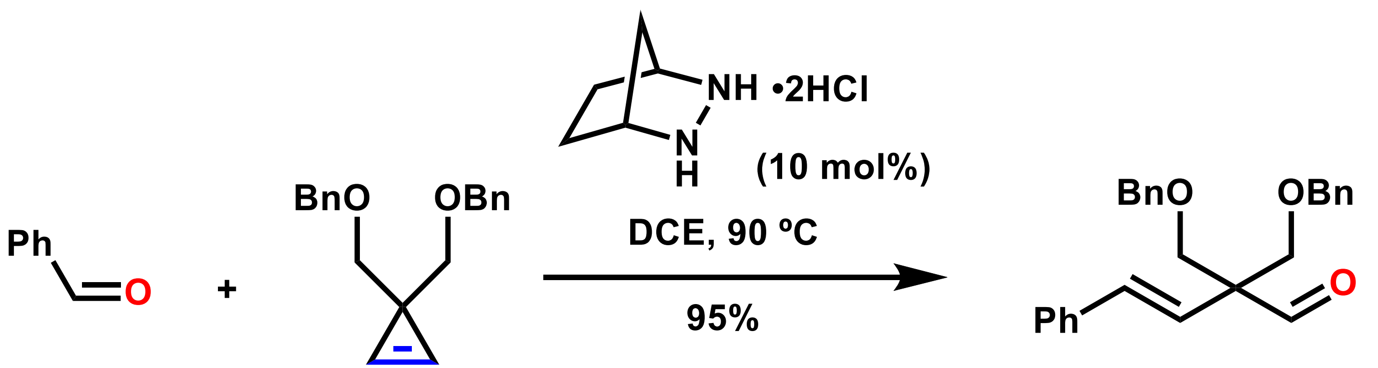




1) Jones, G. II.; Schwartz, S. B..; Marton, M. T. *J. Chem. Soc. Chem. Commun*. **1973**, 374.
2) Valiulin, R. A.; Kutateladze, A. G. *Org. Lett*. **2009**, *11*, 3886.
For detail of these reactions; see also 131005_PS_Hidenori_Todoroki.

Organocatalyzed Carbonyl-Olefin Metathesis

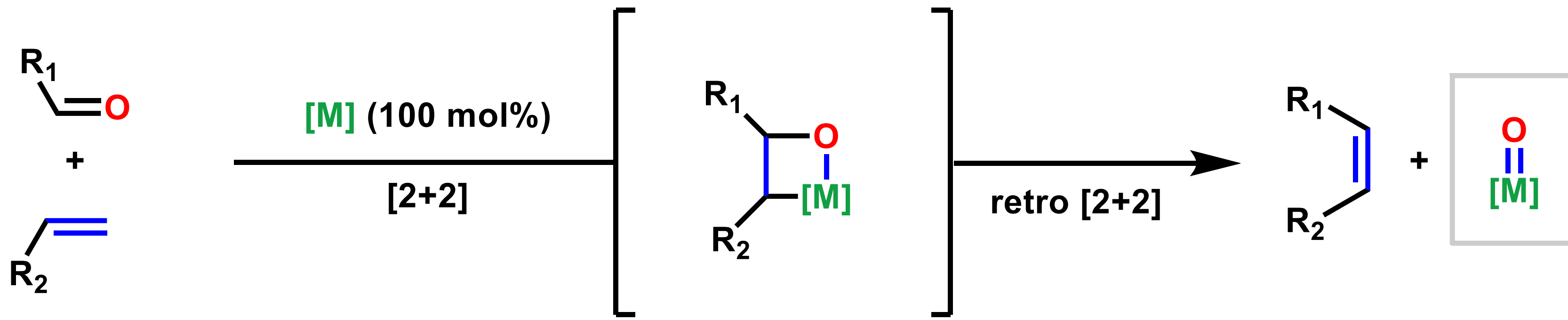


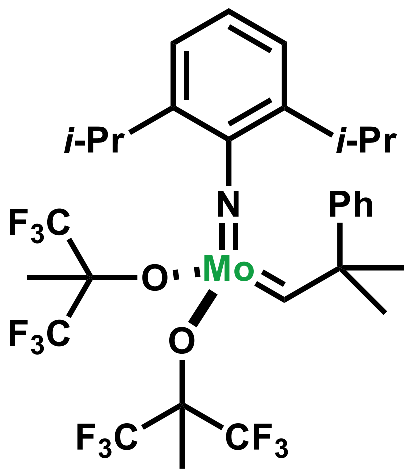


<u>Only highly strained cyclopropenes were applicable as olefinic components.</u>

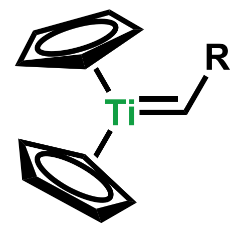
Griffith, A. K.; Vanos, C. M.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, 18581.
For detail of these reactions; see also 131005_PS_Hidenori_Todoroki.

Metal-mediated Carbonyl-Olefin Metathesis





Schrock catalyst



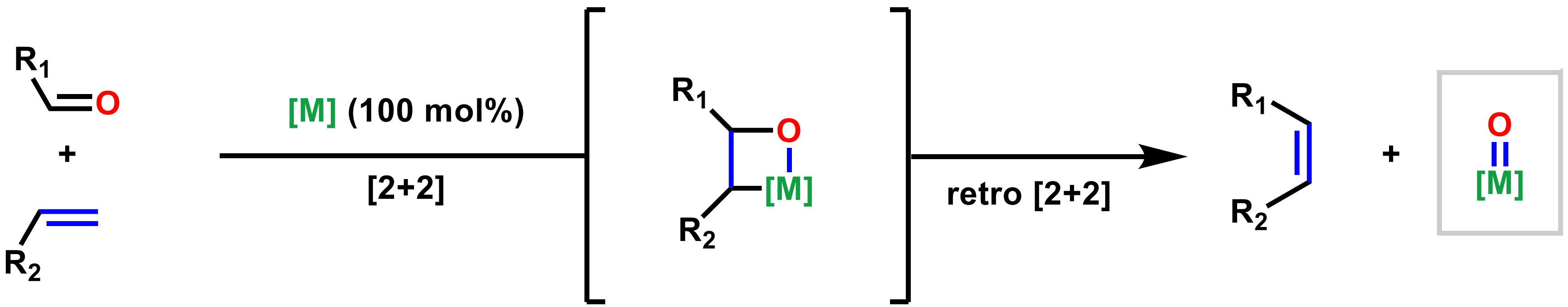
Tebbe reagent
or
Petasis reagent

<u>Due to formation of metal-oxo complex, stoichiometric amount of reagents were required.</u>

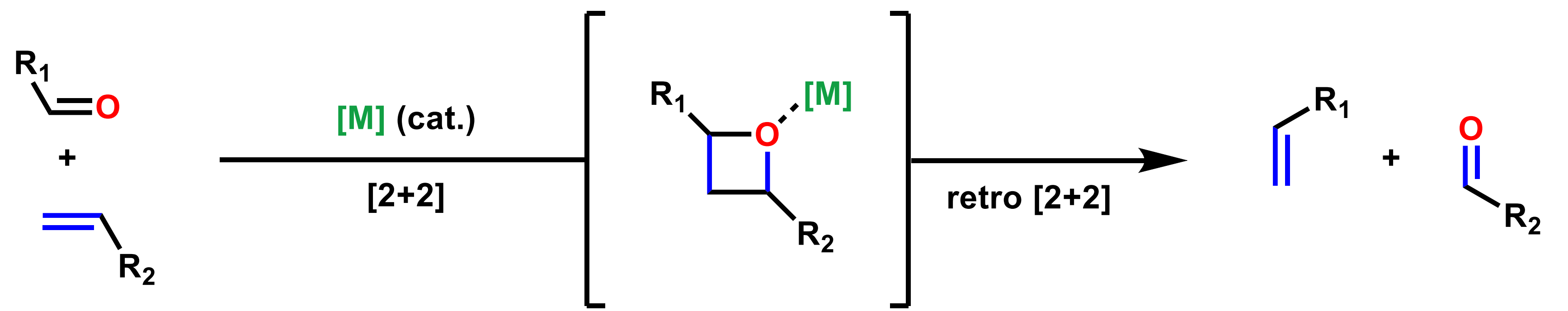
Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843.
Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800.

Design Principle of Lewis Acid Catalyzed Carbon-Olefin Metathesis

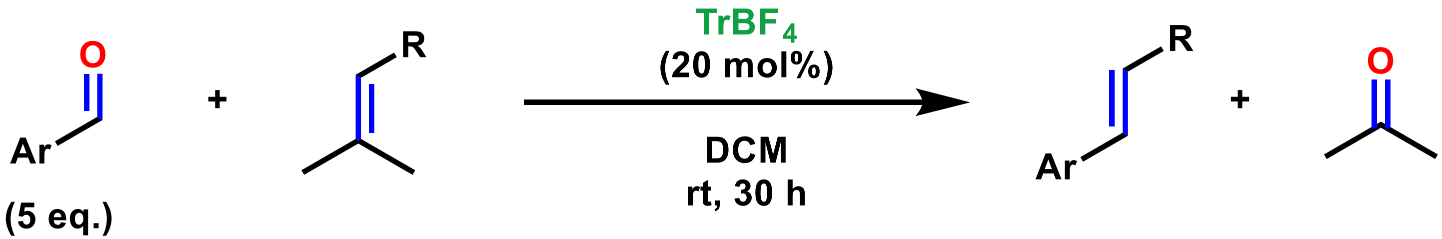
Metal-alkylidene reagents mediated carbonyl-olefin metathesis



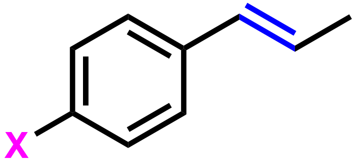
Lewis acid catalyzed carbonyl-olefin metathesis



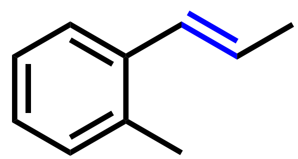
Lewis Acid-catalyzed Carbonyl-Olefin Metathesis



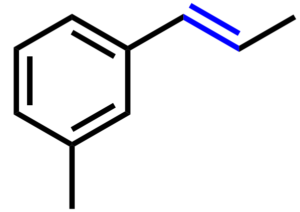
Substrate scope



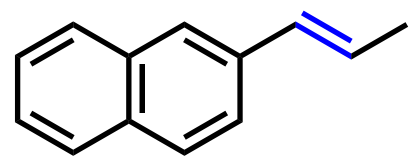
X = H: 68%
X = Me: 55%
X = F: 59%
X = Cl: 54%
X = Br: 55%



85%

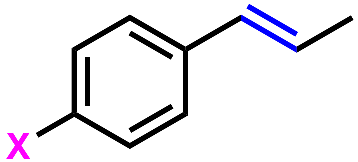


83%

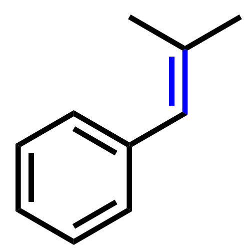


60%

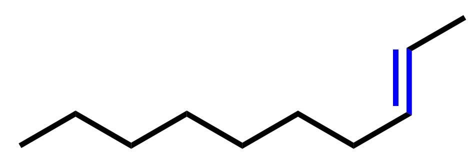
Limitations



X = OMe: >5%
X = NO_2: messy



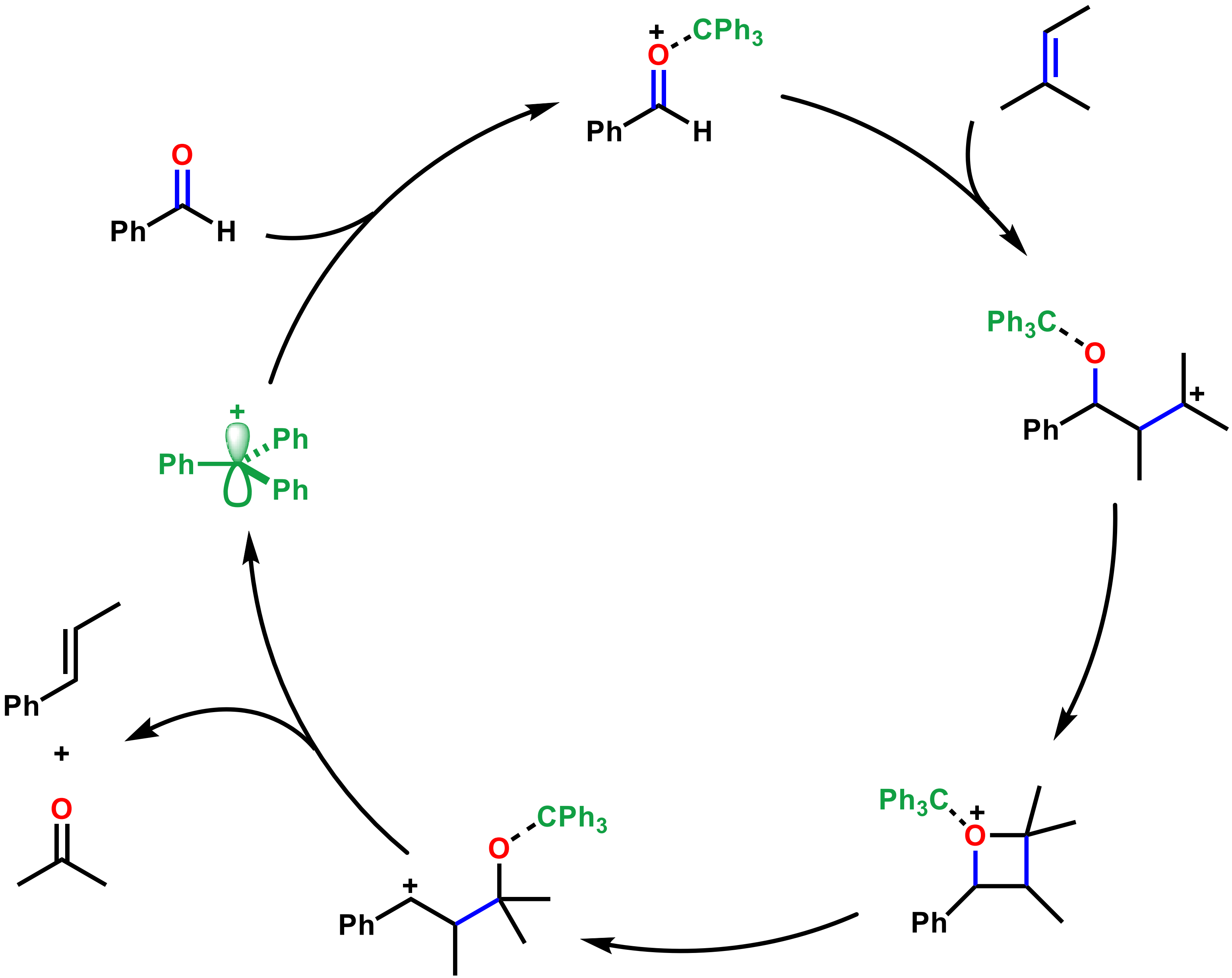
no reaction



decomposition

Naidu, V. R.; Bah, J.; Franzen, J. *Eur. J. Org. Chem.* **2015**, 1834.

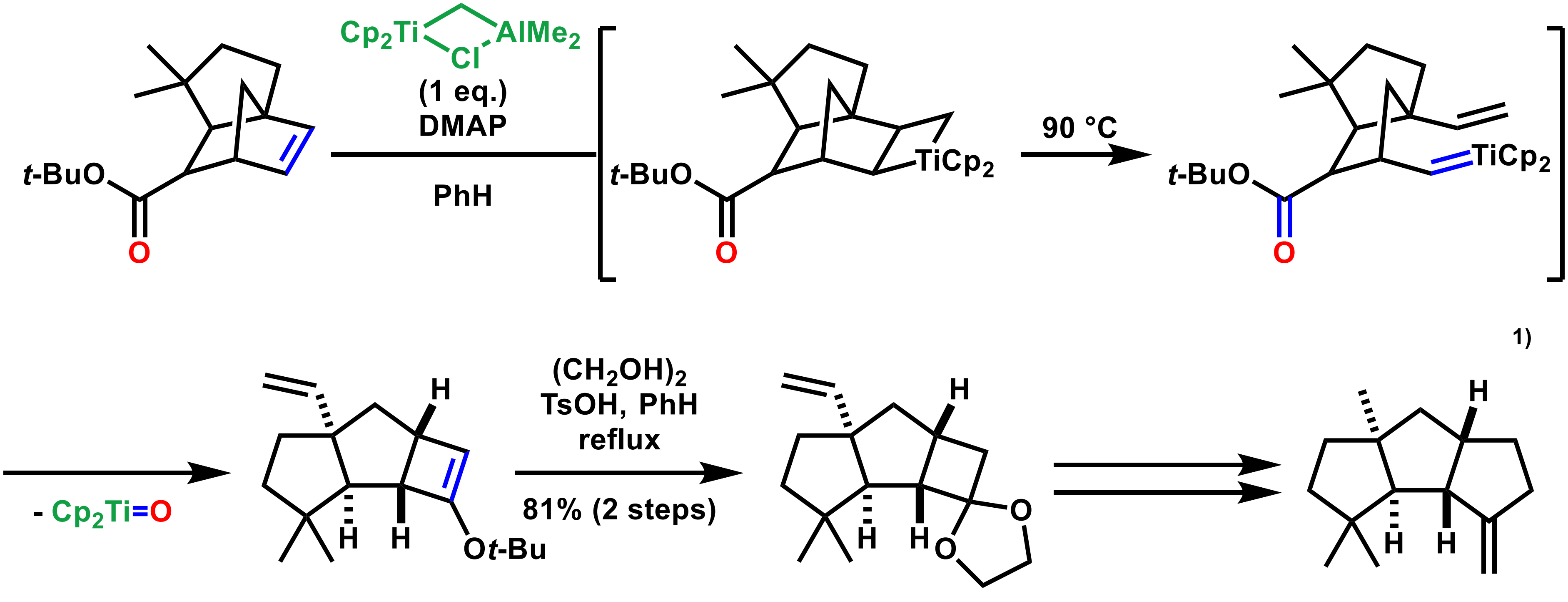
Proposed Mechanism for $TrBF_4$-catalyzed Metathesis



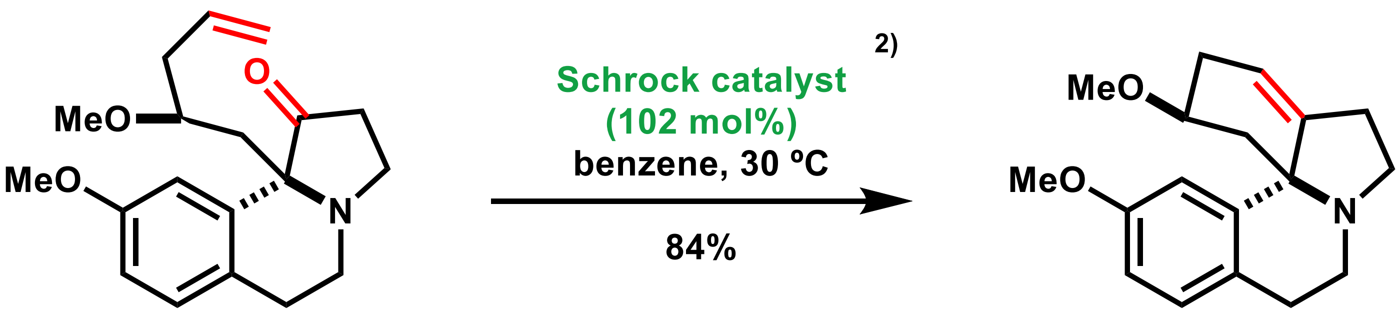
Naidu, V. R.; Bah, J.; Franzen, J. *Eur. J. Org. Chem.* **2015**, 1834.

Application to Total Synthesis

Only a few examples of application to total synthesis has been reported.



(±)-Δ$^{(9,12)}$-capnellene



cocculidine

1) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843.
2) Heller, S. T.; Kiho, T.; Narayan, A. R. H.; Sarpong, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 11129.

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Prof. Corinna S. Schindler

1999 – 2004: Technical University of Munich
(Diploma; German Equivalent M.Sc.: Prof. K.C. Nicolau)

2005 – 2010: ETH Zurich (Ph.D.: Prof. Erick M. Carreira)

2010 – 2013: Harvard University (Postdoc: Prof. Eric N. Jacobsen)

2013 – : University of Michigan (Assistant Professor)

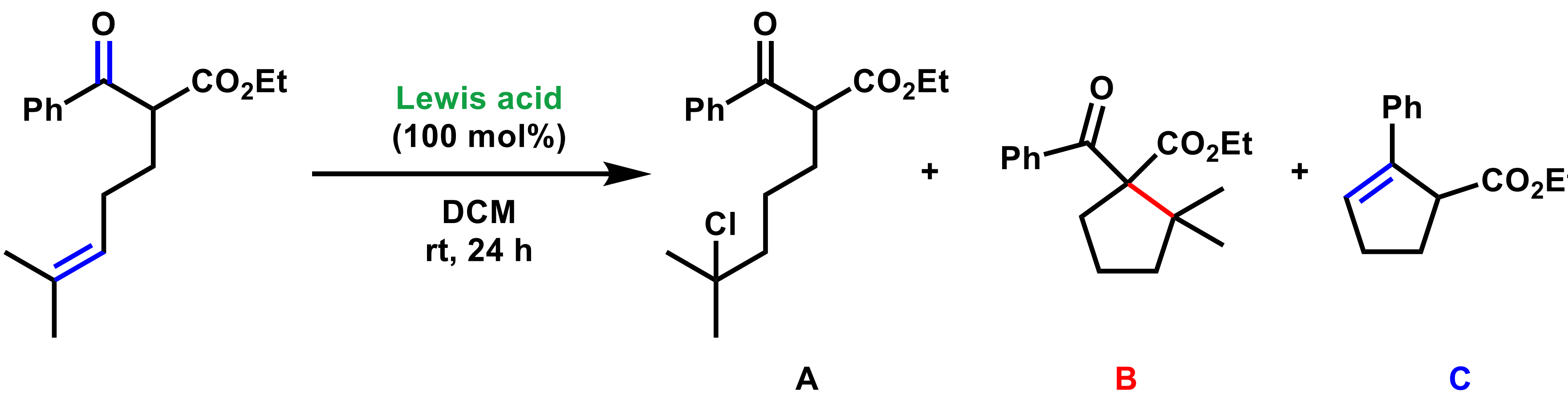
Research area:

1. Development of catalysis with environmentally benign metals.

2. Total synthesis of biological active natural compounds.

3. Biological application of synthesized natural compounds.

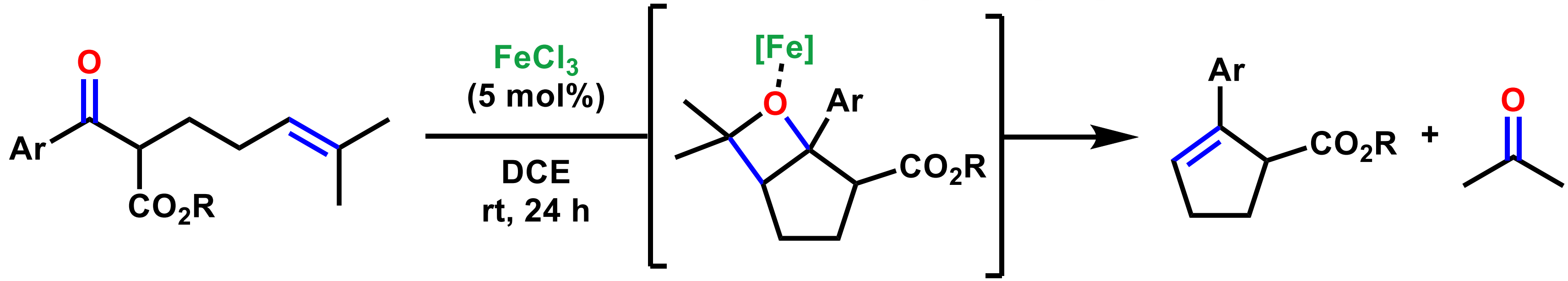
Stoichiometric Lewis Acid Evaluation

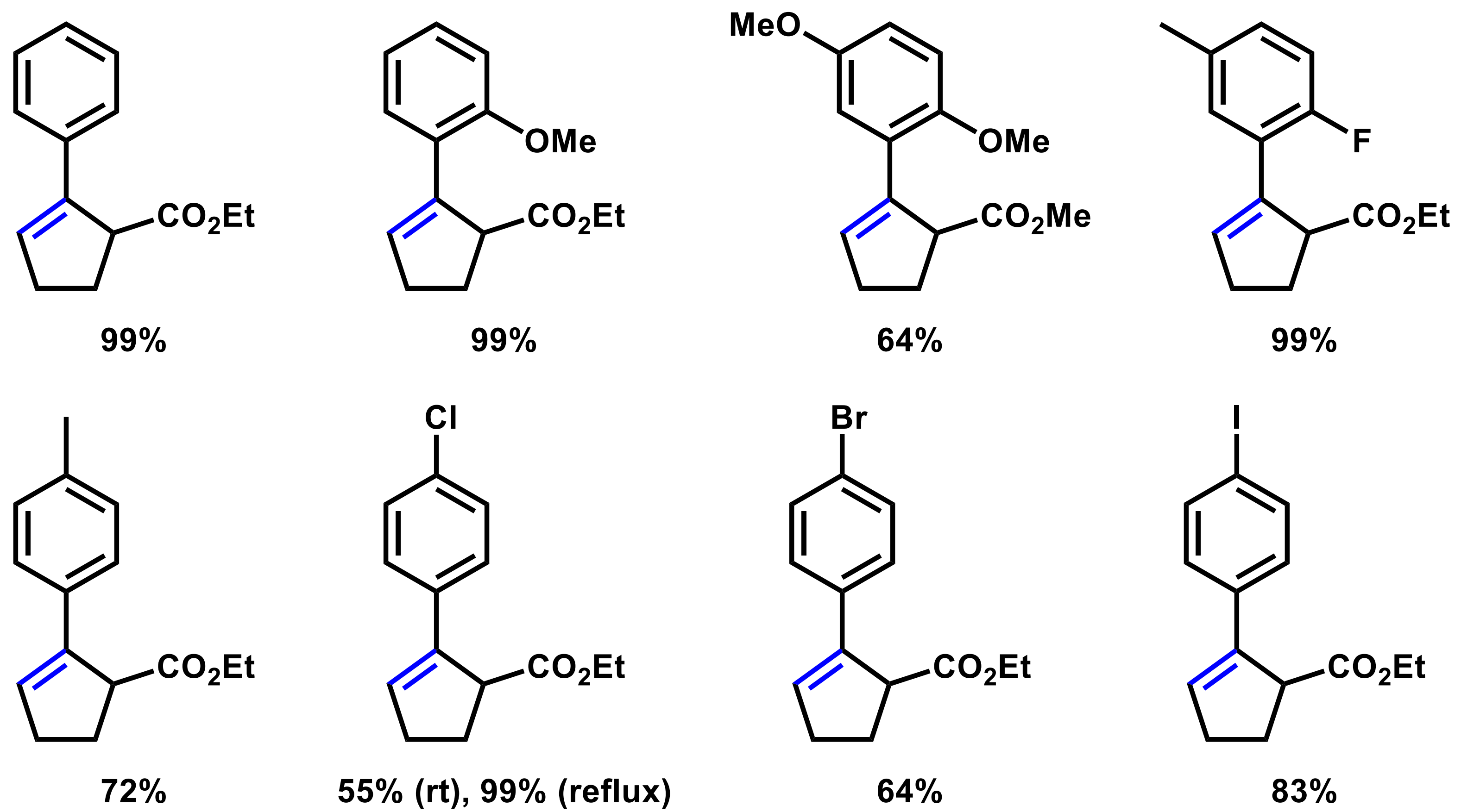


Lewis acid	A	B	C
$AlCl_3$	66%	-	-
$TiCl_4$	-	74%	-
$SnCl_4$	-	47%	24%
$FeCl_3$	-	-	50%

Ludiwig, J. R.; Zimmerman, P. M.; Gianino, J. B.; Schindler, C. S. *Nature* **2016**, *533*, 374.

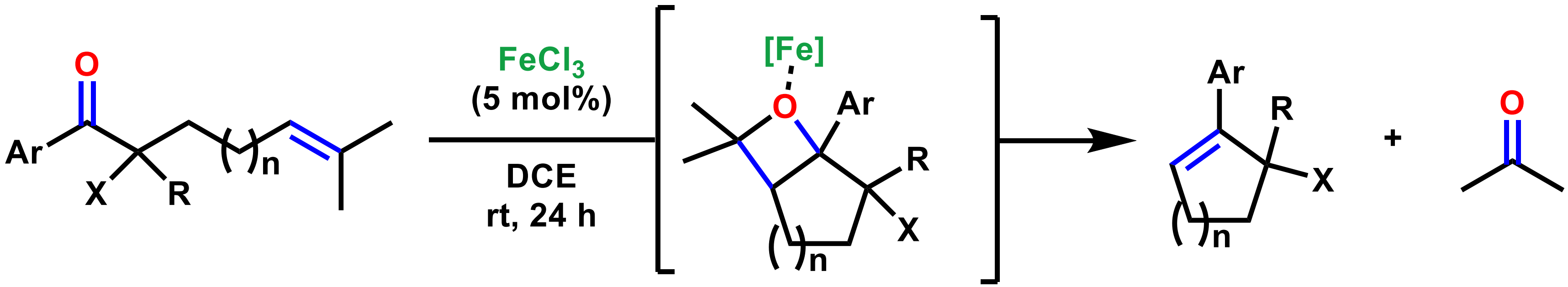
Substrate Scope (1)

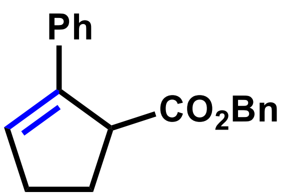




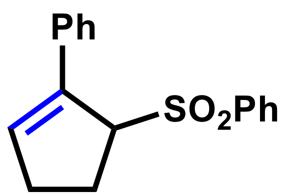
Ludiwig, J. R.; Zimmerman, P. M.; Gianino, J. B.; Schindler, C. S. *Nature* **2016**, *533*, 374.

Substrate Scope (2)

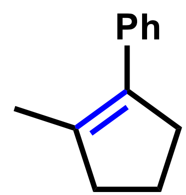




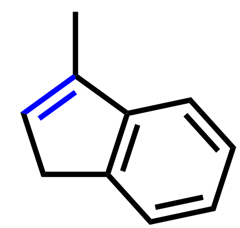
67%



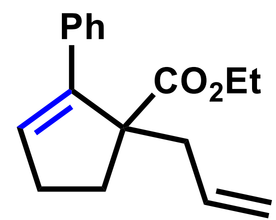
66%



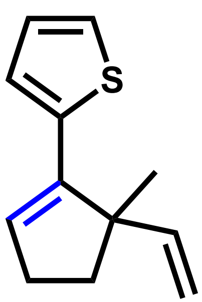
52%



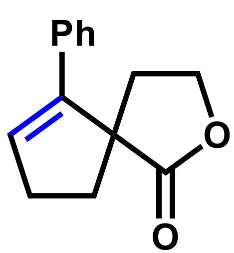
93%



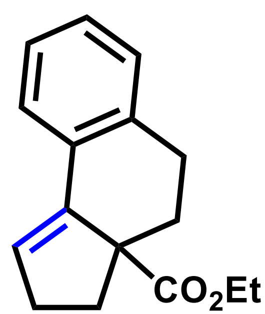
99%



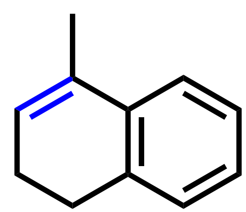
76%



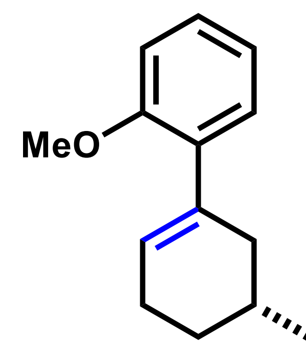
87%



85%



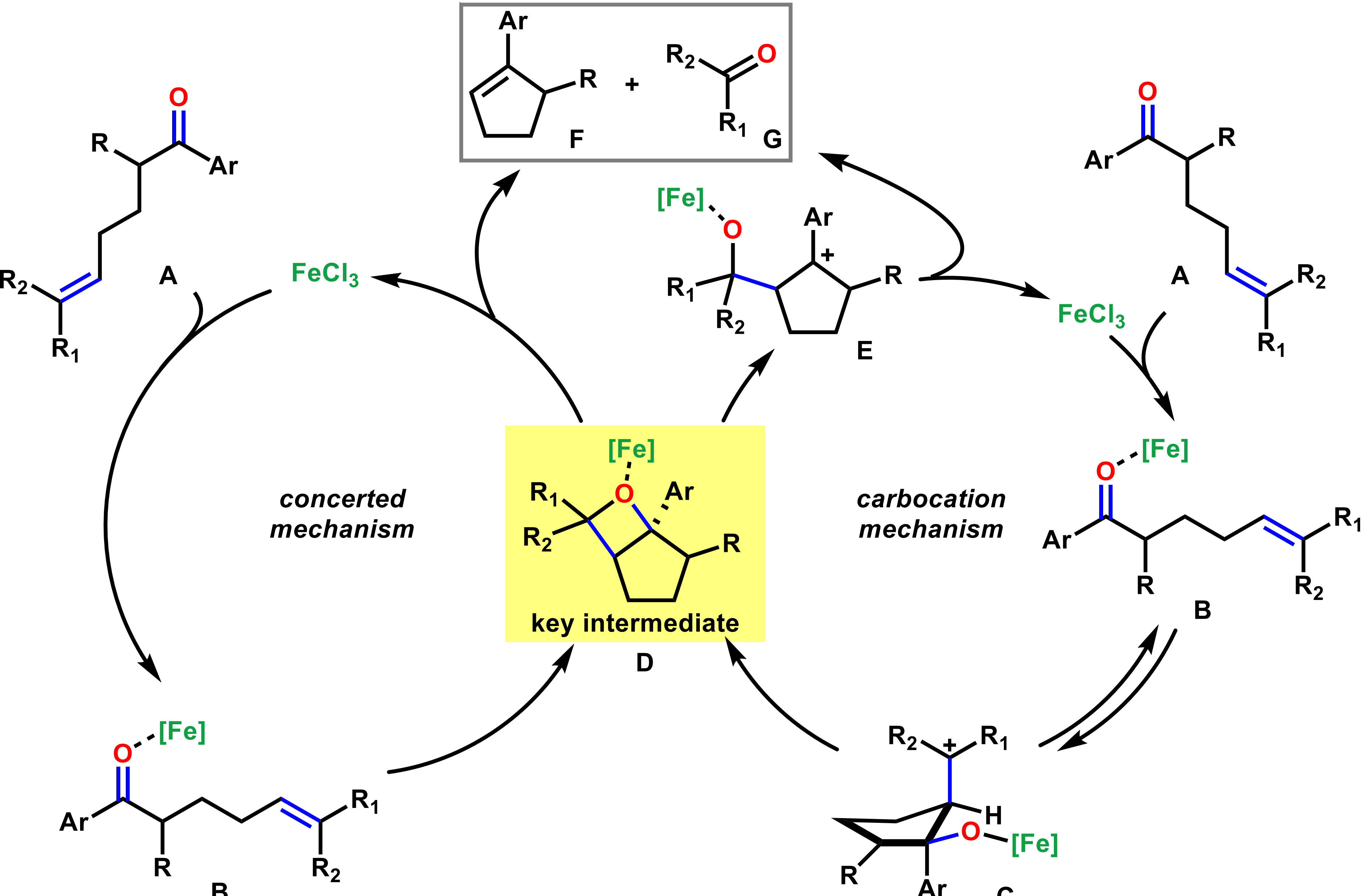
70%



71%

Ludiwig, J. R.; Zimmerman, P. M.; Gianino, J. B.; Schindler, C. S. *Nature* **2016**, *533*, 374.

Mechanism Hypothesis



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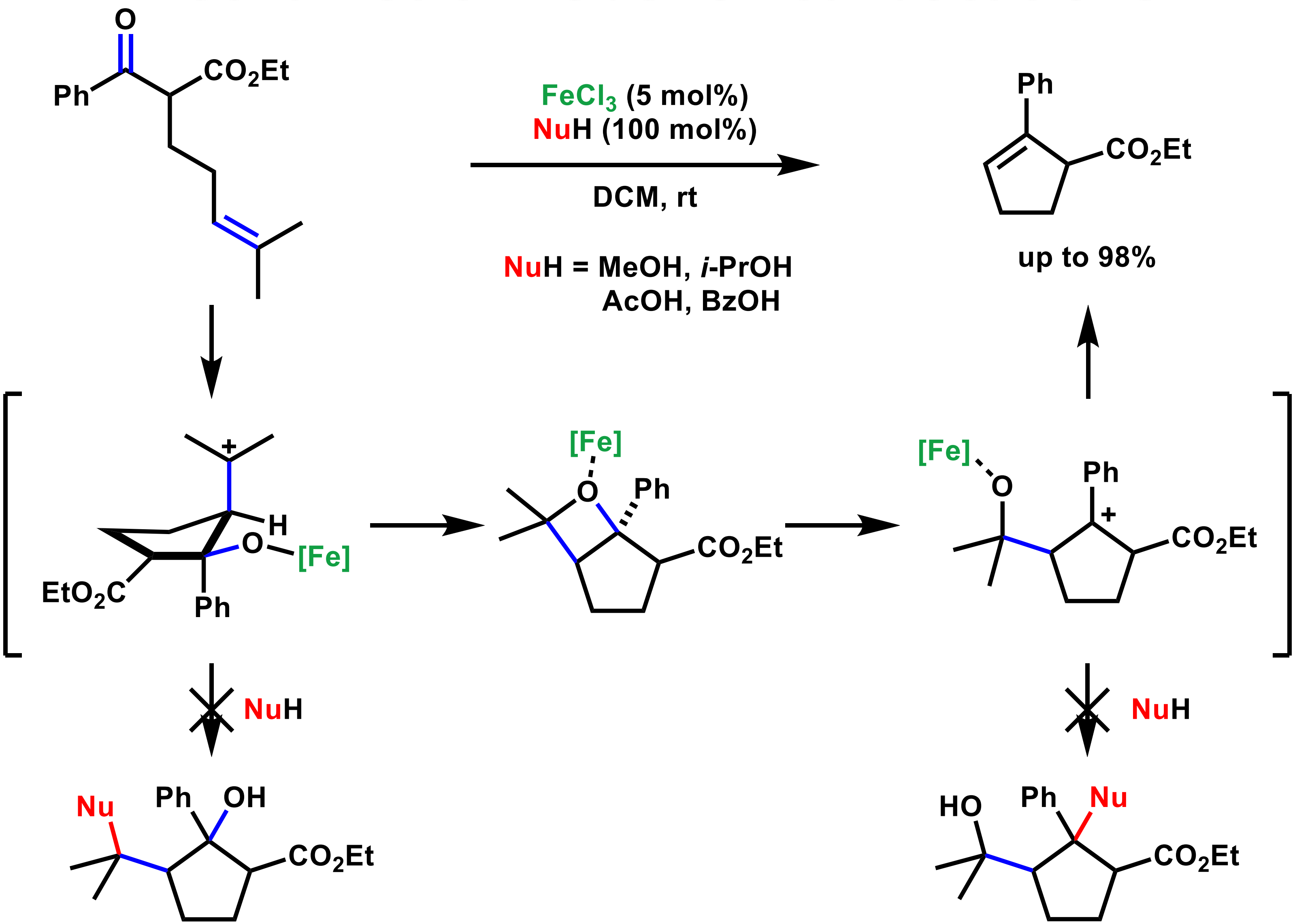
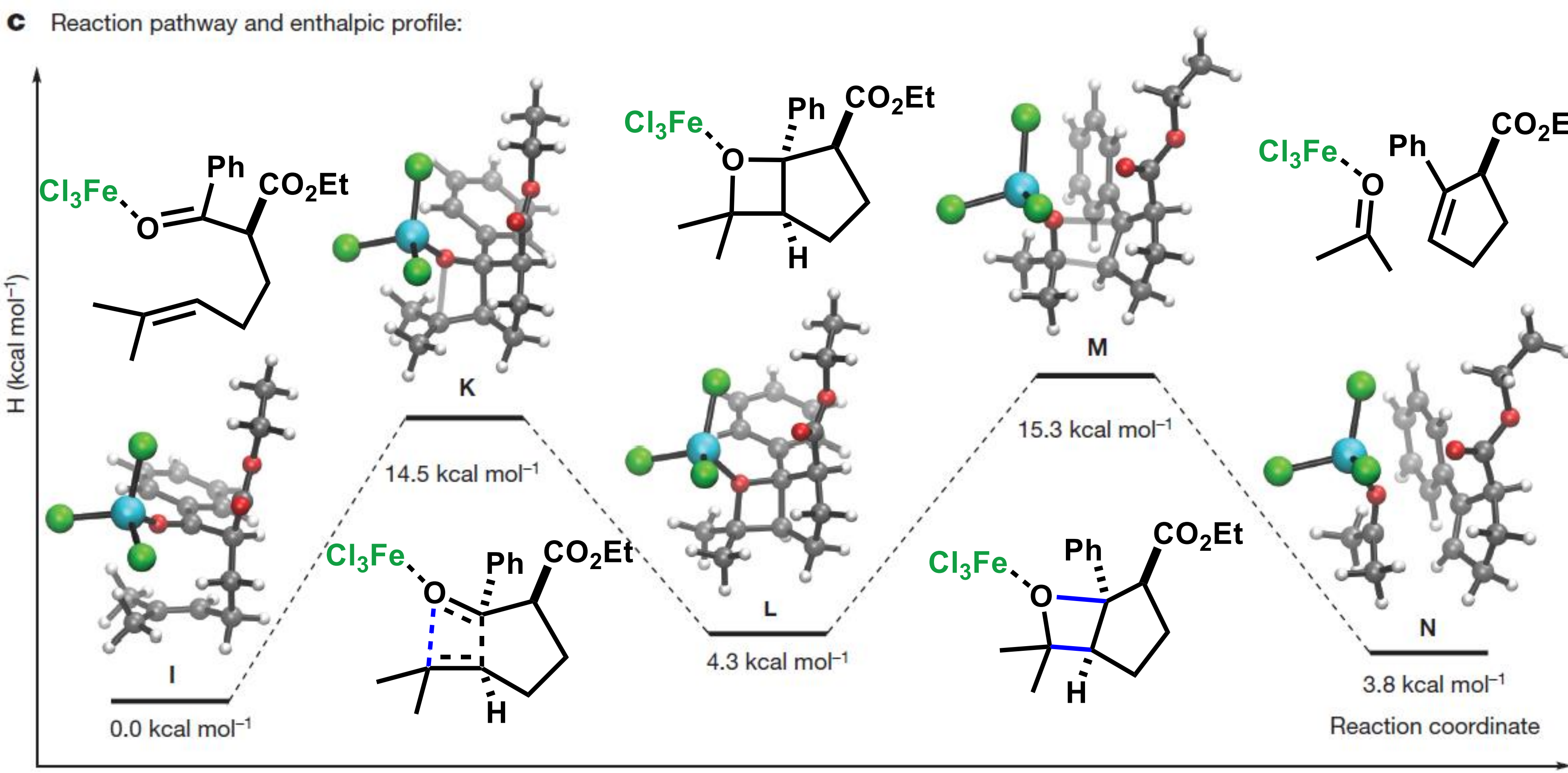
Mechanistic Probe for Carbocations



Carbocations seemed not to be essential intermediates for the reaction;
The reaction proceeded via a concerted mechanism?

Ludiwig, J. R.; Zimmerman, P. M.; Gianino, J. B.; Schindler, C. S. *Nature* **2016**, *533*, 374.

Computationally Proposed Pathway



UB97-D/6-31G* without solvent

<u>**The reaction seemed to proceed via concerted, asynchronous pathway**</u>

Ludiwig, J. R.; Zimmerman, P. M.; Gianino, J. B.; Schindler, C. S. *Nature* **2016**, *533*, 374.

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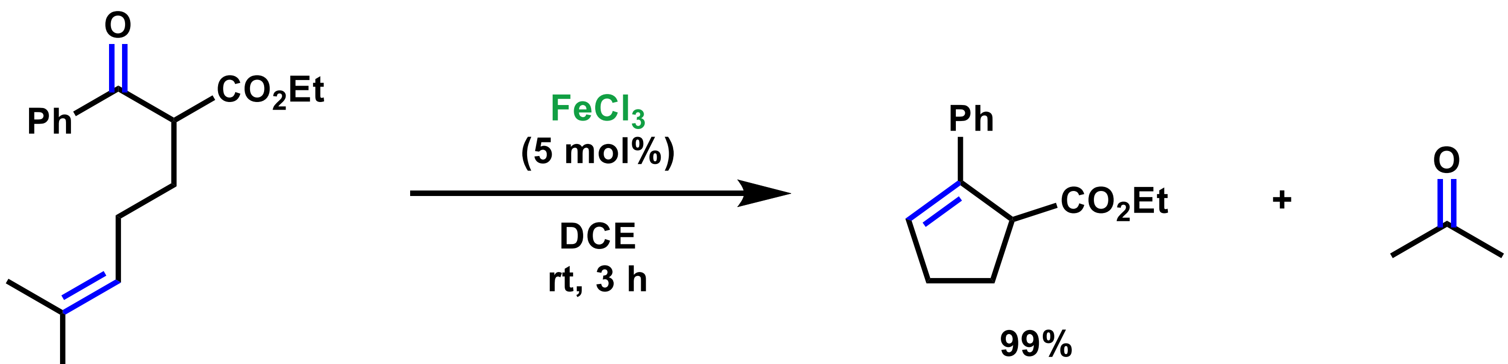
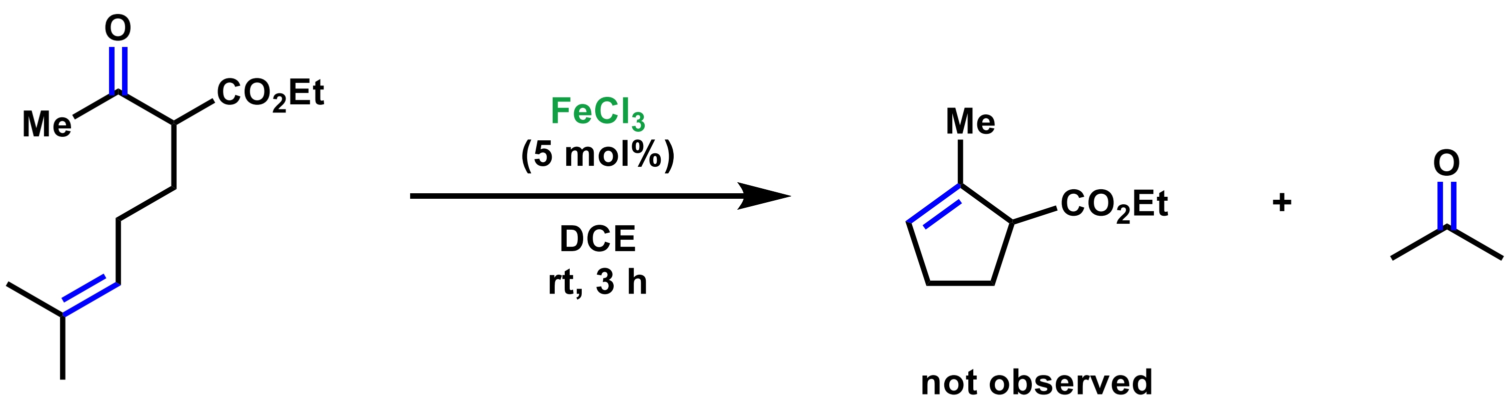
Failure of Metathesis of Aliphatic Ketones

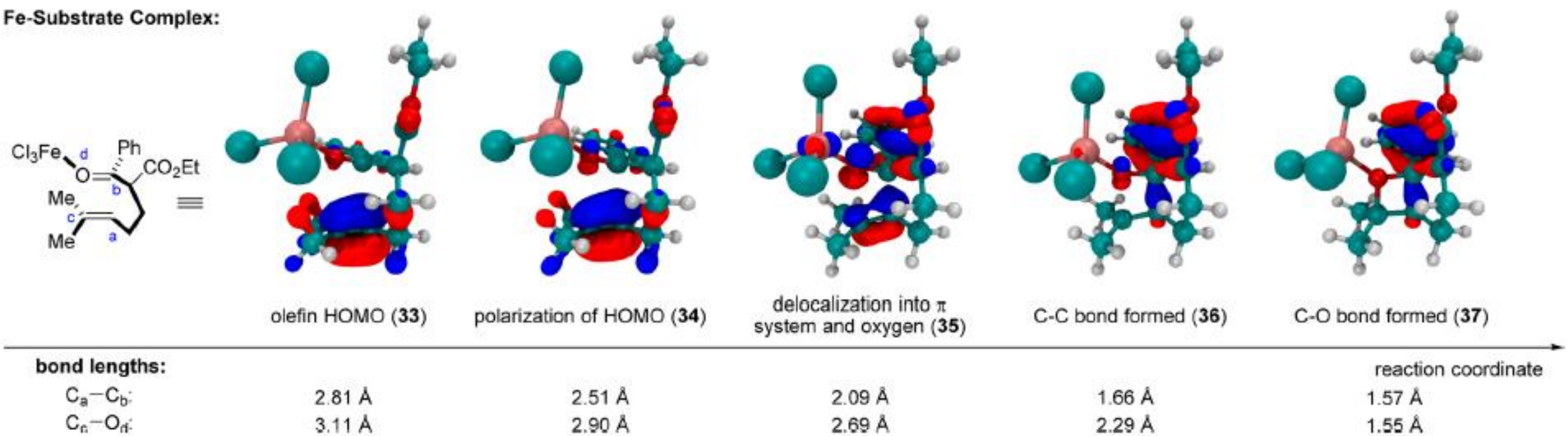




Albright, D.; Riehl, P. S.; McAtee, C. C.; Reid, J. P.; Ludwig, J. R.; Karp, L. A.; Zimmerman, P. M.; Sigman, M. S.; Schindler, C. S. *J. Am. Chem. Soc.* **2019**, *141*, 1690.

Importance of Aryl Group for Metathesis

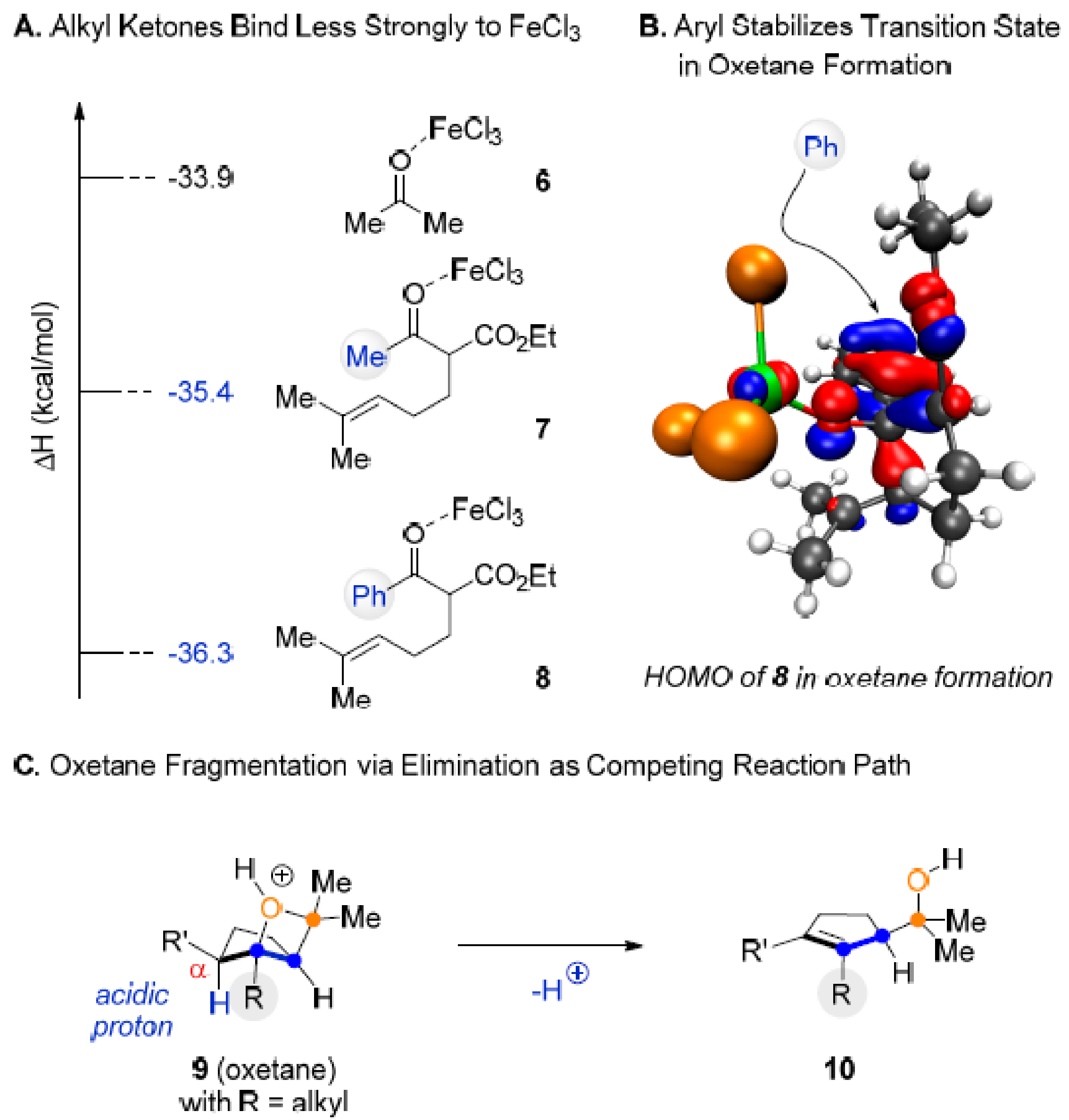
HOMO of Fe-Substrate complex during oxetane formation



<u>**Aryl π system plays an important role in stabilization of transition state**</u>

Ludiwig, J. R.; Phan, S.; McAtee, C. C.; Zimmerman, P. M.; Devery, III, J. J.; Schindler, C. S. *J. Am. Chem. Soc.* **2017**, *139*, 10832.

Challenges Associated with Aliphatic Ketones



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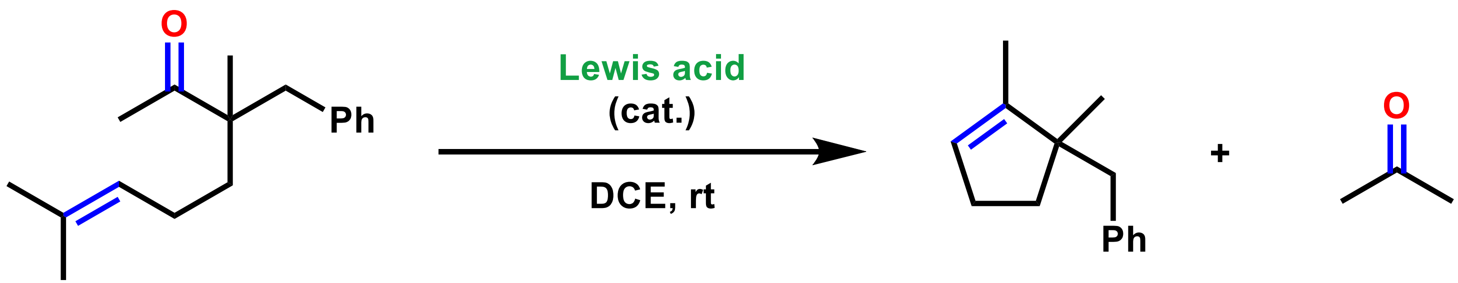
Lewis Acid Evaluation



entry	Lewis acid	mol%	time	yield (%)	conv. (%)
1	$AlCl_3$	5	24 h	0	0
2	EASC	100	15 min	30	100
3	$TiCl_4$	5	24 h	0	36
4	$GaCl_3$	5	16 h	21	82
5	$SnCl_4$	5	16 h	30	70
6	BF_3•OEt_2	5	24 h	24	51
7	$FeCl_3$	5	15 min	44	48
8	$FeCl_3$	10	24 h	74	78

EASC = ethyl aluminum sesquichloride

Albright, D.; Riehl, P. S.; McAtee, C. C.; Reid, J. P.; Ludwig, J. R.; Karp, L. A.; Zimmerman, P. M.; Sigman, M. S.; Schindler, C. S. *J. Am. Chem. Soc.* **2019**, *141*, 1690.

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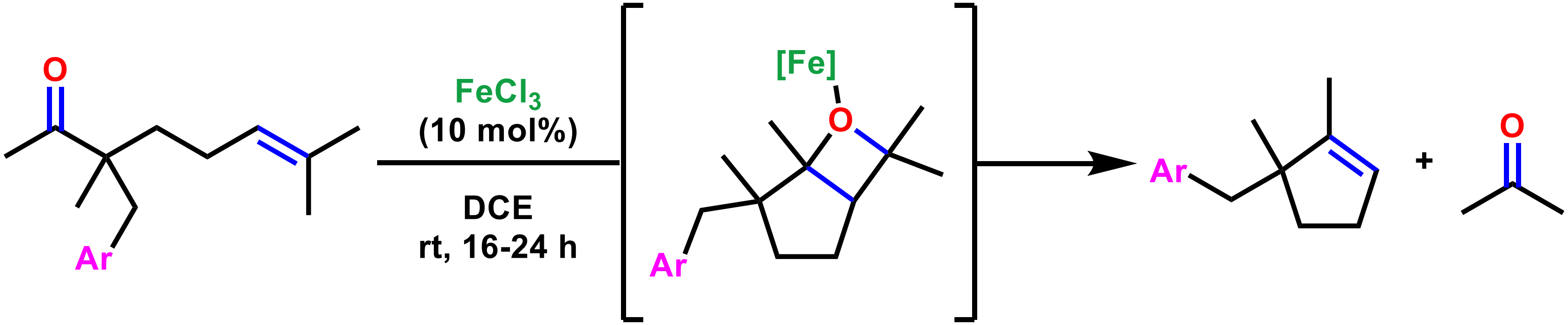
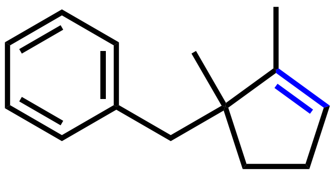
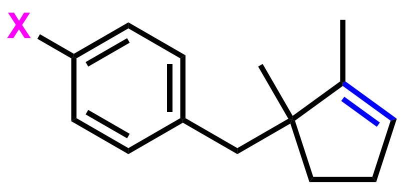
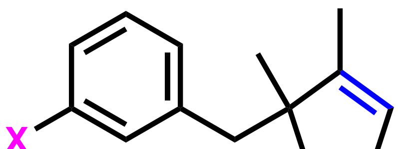




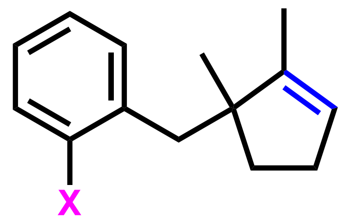
74% (99% brsm)



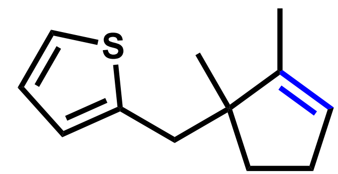
X = F: 63% (94% brsm)
X = Cl: 75% (99% brsm)
X = CF_3: 72%*
X = CN: 93% (99% brsm)*
X = NO_2: 84%*
X = Br: 16%
X = Me: 94% (97% brsm)*
X = *i*-Pr: 85% (98% brsm)*
X = *t*-Bu: 68%*
X = OMe: 38% (93% brsm)*



X = F: 73% (94% brsm)
X = Cl: 72%
X = OMe: 64% (83% brsm)
X = Me: 30% (50% brsm)



X = Me: 63% (99% brsm)*
X = Cl: 50% (99% brsm)*

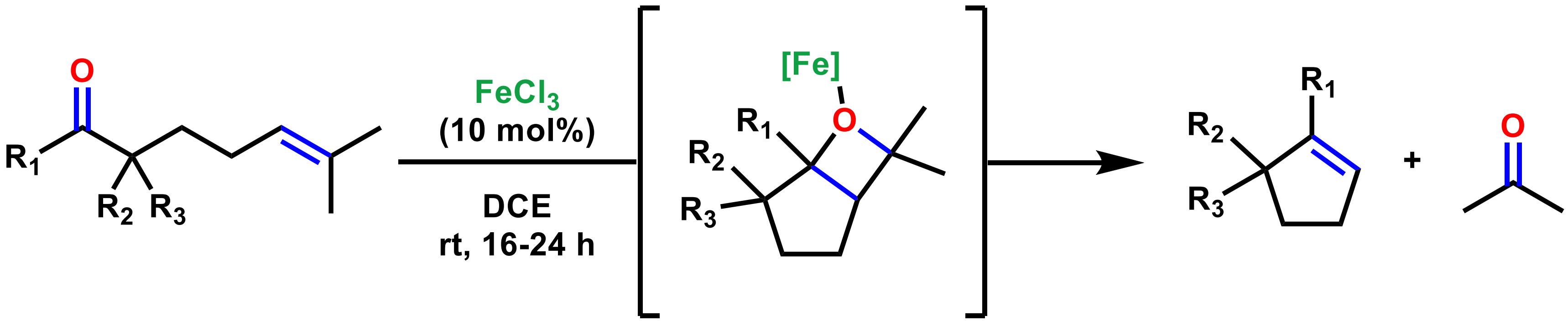


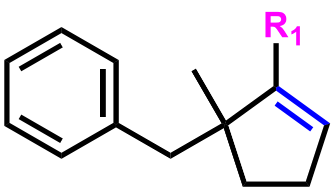
64% (83% brsm)

* 80 °C for 3 h

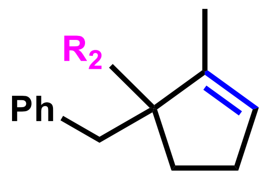
Albright, D.; Riehl, P. S.; McAtee, C. C.; Reid, J. P.; Ludwig, J. R.; Karp, L. A.; Zimmerman, P. M.; Sigman, M. S.; Schindler, C. S. *J. Am. Chem. Soc.* **2019**, *141*, 1690.

Substrate Scope (2)

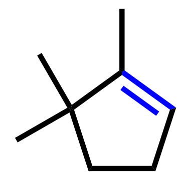




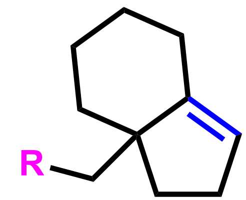
R_1 = Et: 34%
R_1 = *i*-Bu: 62%*



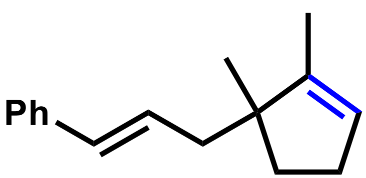
R_2 = Bn: 72%*
R_1 = *c*-Pr: 58%*



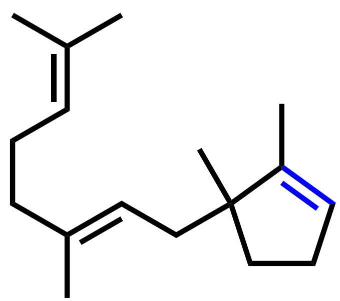
56%*



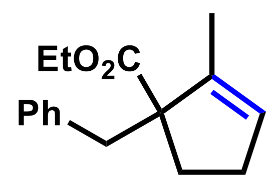
R = H: 38%*
R = Ph: 78%*
R = tol: 70%*



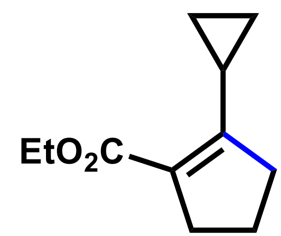
60% (99% brsm)*



31% (77% brsm)*



28%*



20%

* 80 °C for 3 h

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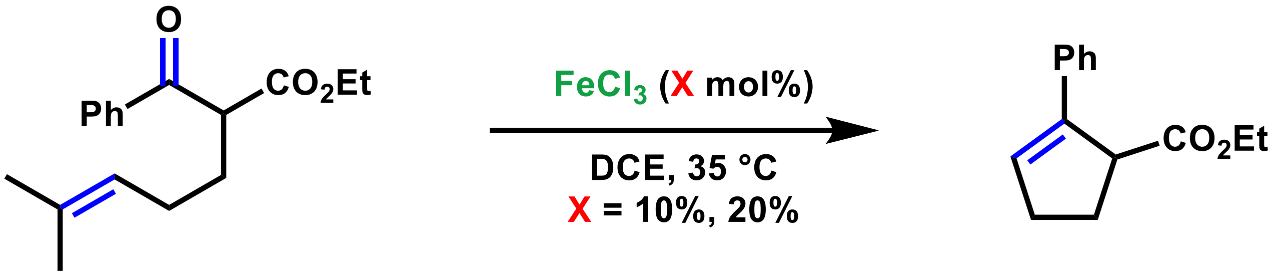
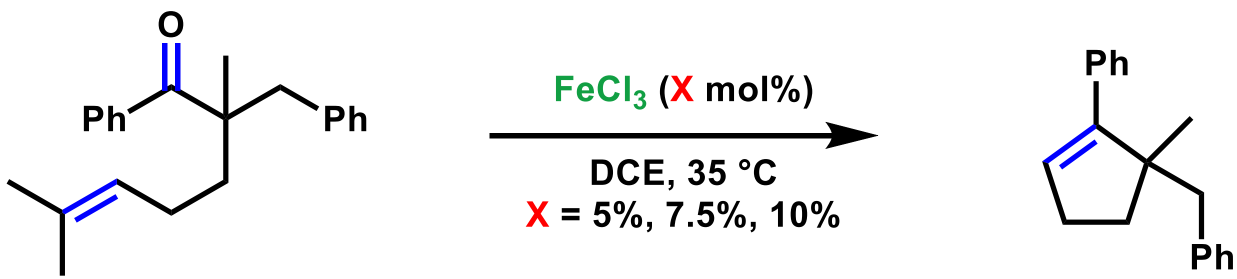
Kinetic Investigations of Metathesis



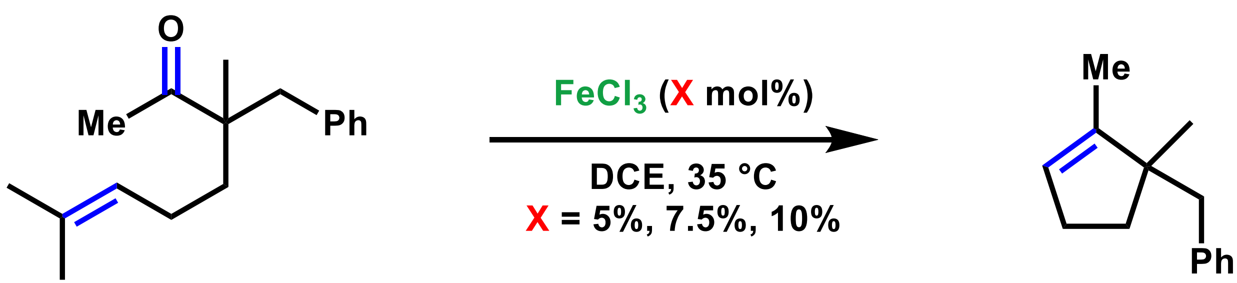
zero-order in SM

order in $FeCl_3$: **1.11 ± 0.15**



zero-order in SM

order in $FeCl_3$: **1.22 ± 0.20**



zero-order in SM

order in $FeCl_3$: **1.78 ± 0.18**

Two equivalent of $FeCl_3$ seemed to be involved in the reaction.

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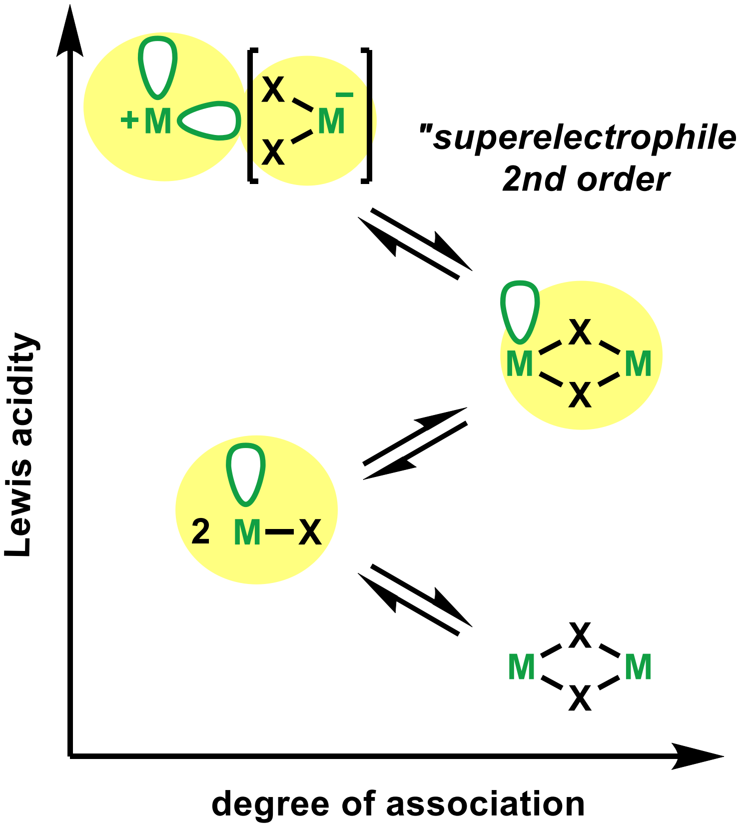
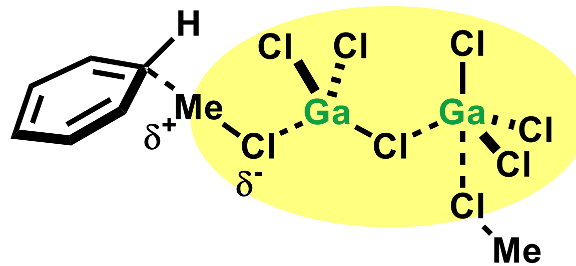
Lewis Acid Activation Mode: “Superelectrophile”

- Relationship between Lewis acidity and state of association

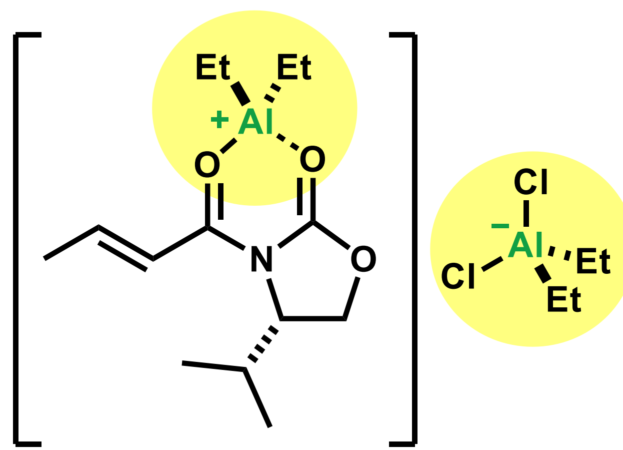


Heterobiometallic association of two Lewis acids [1]
(e.g. B, Al, Zr, Ti) is more common than homobimetallic association.

- Friedel-Crafts alkylation of benzene was second order in $GaCl_3$ (Brown, 1969)[2]



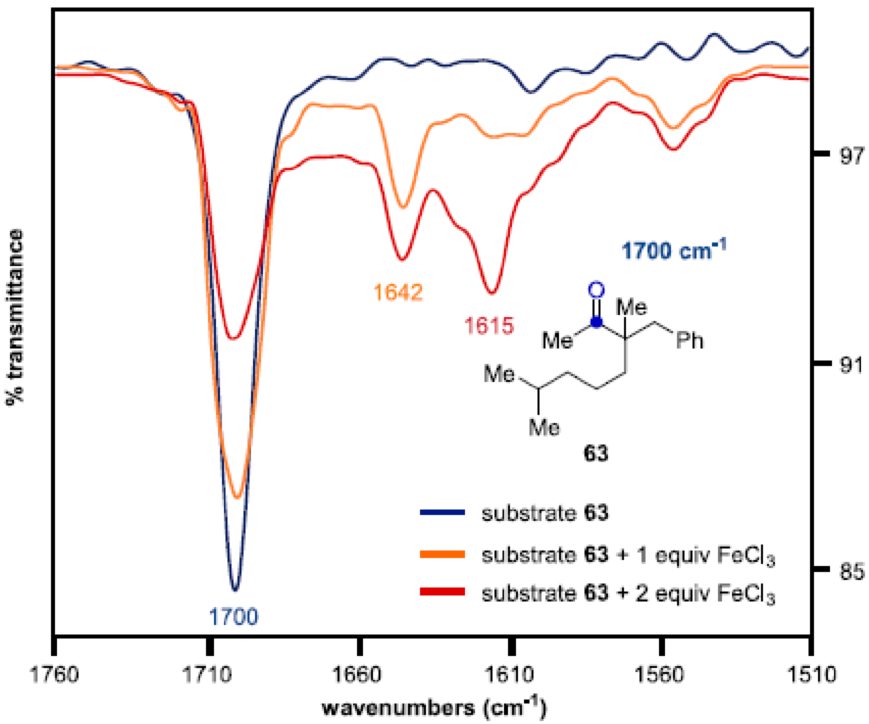
- Ionic complex of Et_2AlCl_2 and dienophile in Diels-Alder reaction (Evans, 1988)[3]



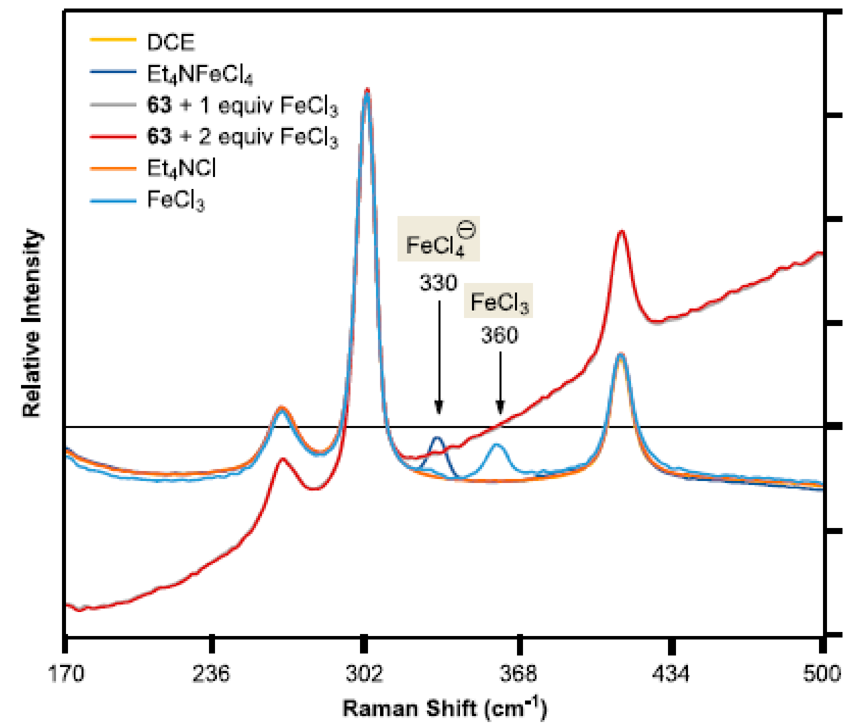
1) Negishi, E. *Pure Appl. Chem*. **1981**, *53*, 2333.
2) DeHaan, F. P.; Brown, H. C. *J. Am. Chem. Soc.* **1969**, *91*, 4844.
3) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1283.

Spectroscopic Measurement of Fe-Dimer

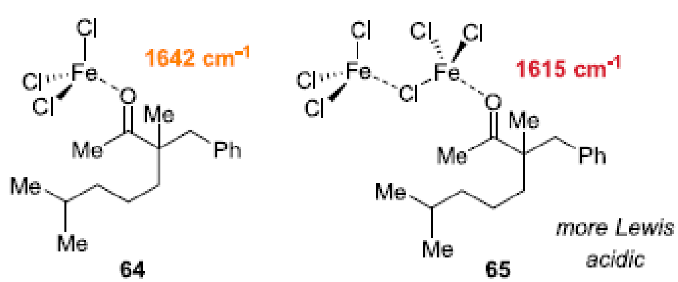
A. IR Spectroscopic Measurements Support Iron-Dimer



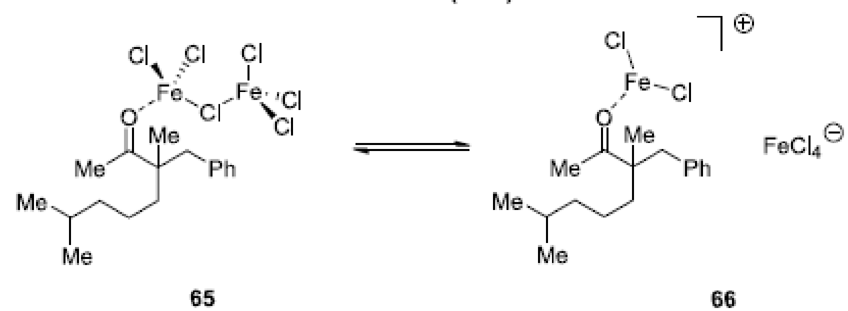
C. Raman Spectroscopic Measurements Support Iron-Dimer



B. Calculations Support IR Results



Δ(measured) = 27 cm^{-1} vs. Δ(calculated) = 20.02 cm^{-1}



single bridged **ion pair**

Both are second order in $FeCl_3$

Singly bridged $FeCl_3$ dimers might be active catalytic species

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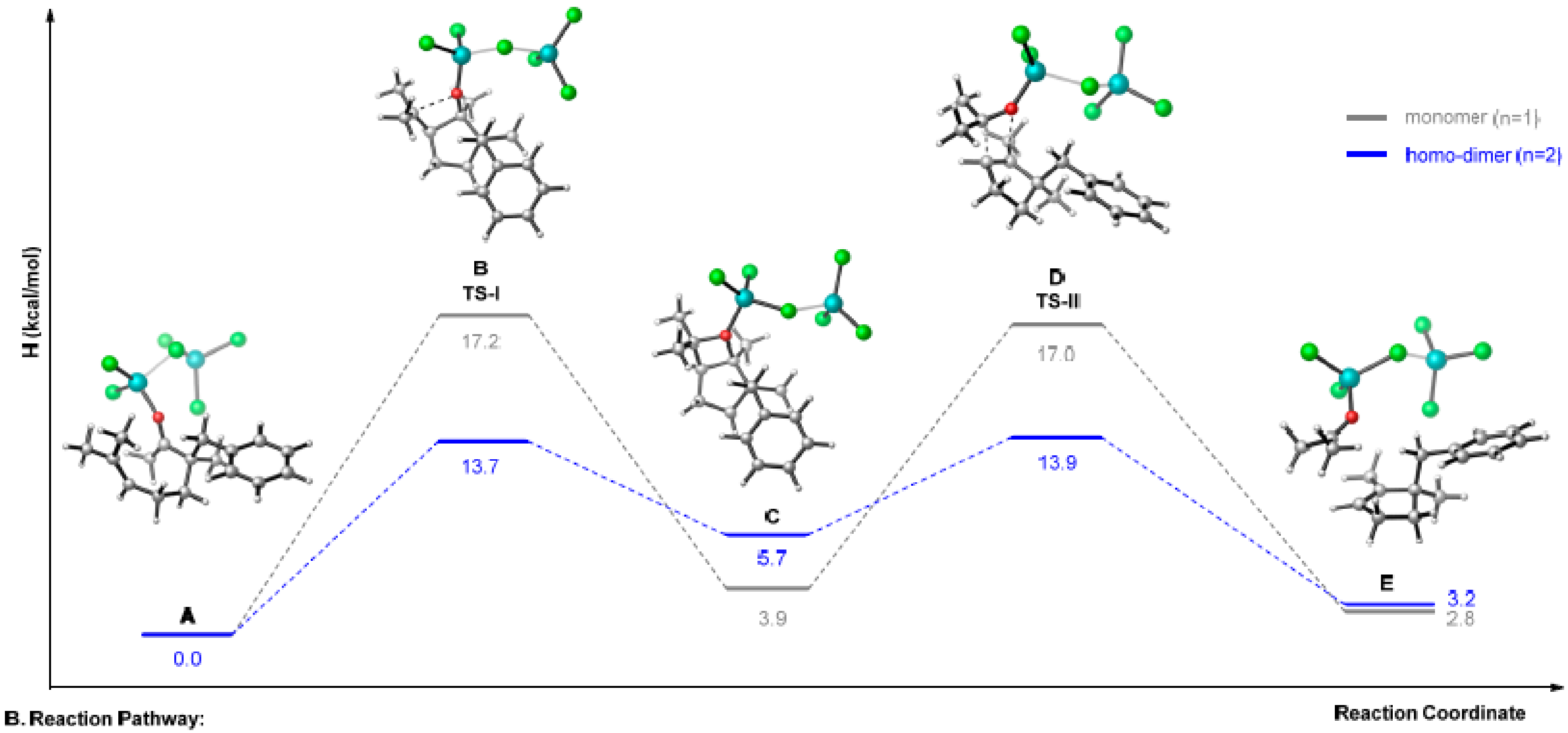
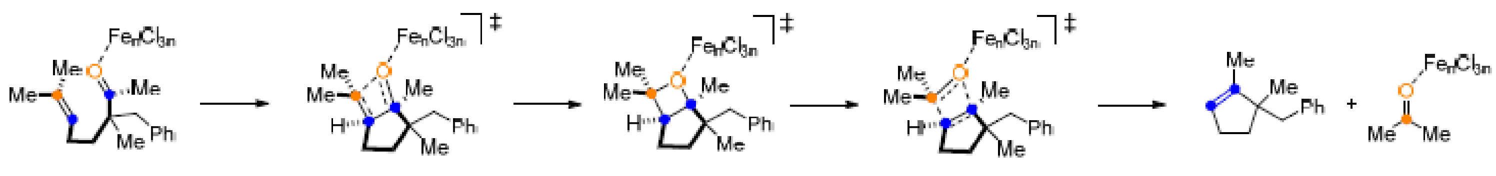
Computational Study of Reaction Pathway

A. Enthalpic Profile:



B. Reaction Pathway:



activation mode	A*	B (TS-I)*	C*	D (TS-II)*	E*
monomer (n=1)	0.0	17.2	3.9	17.0	2.8
homo-dimer (n=2)	0.0	13.7	5.7	13.9	3.2

*values refer to enthalpies H in kcal/mol.

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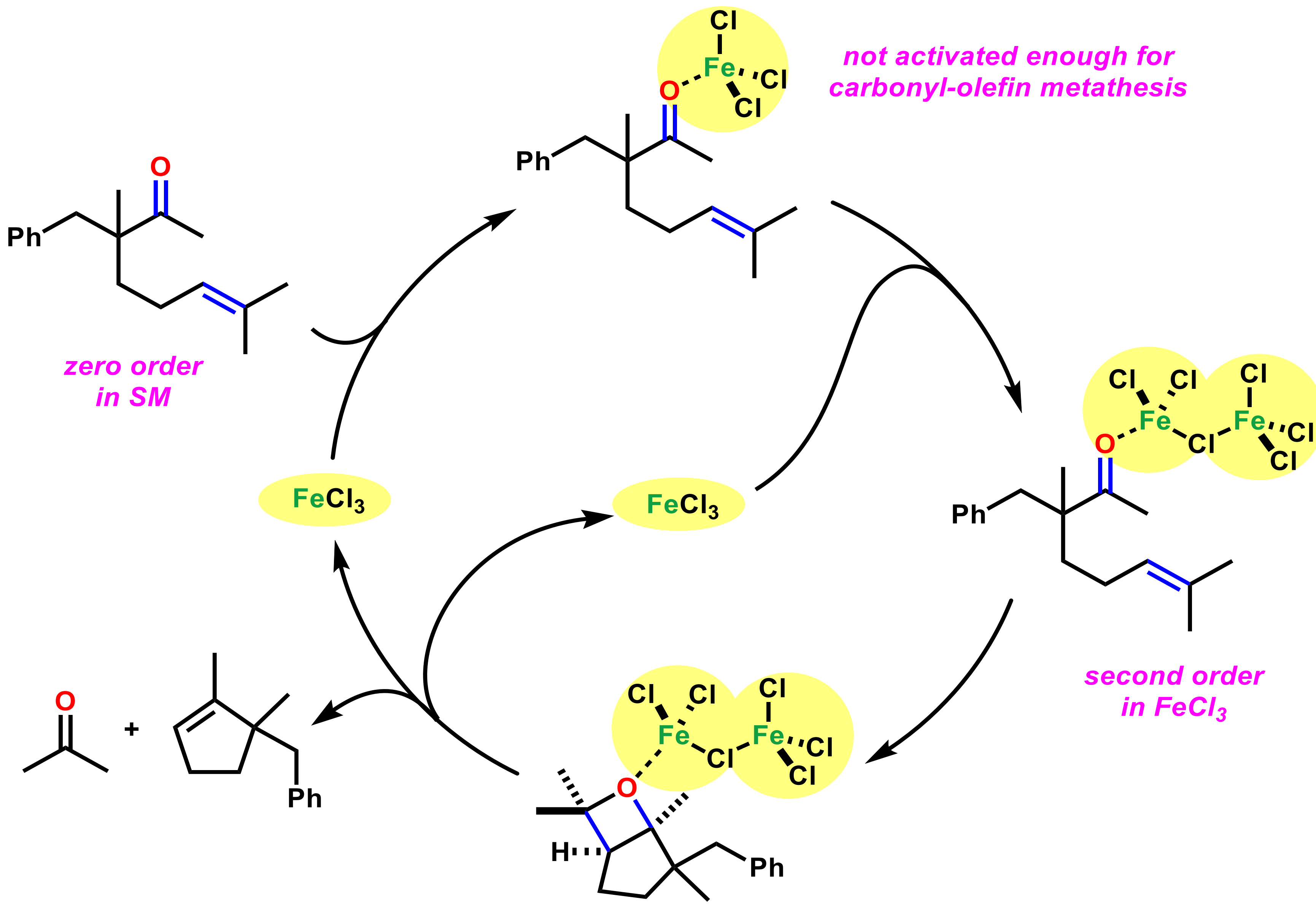
Proposed Reaction Pathway for Aliphatic Ketones



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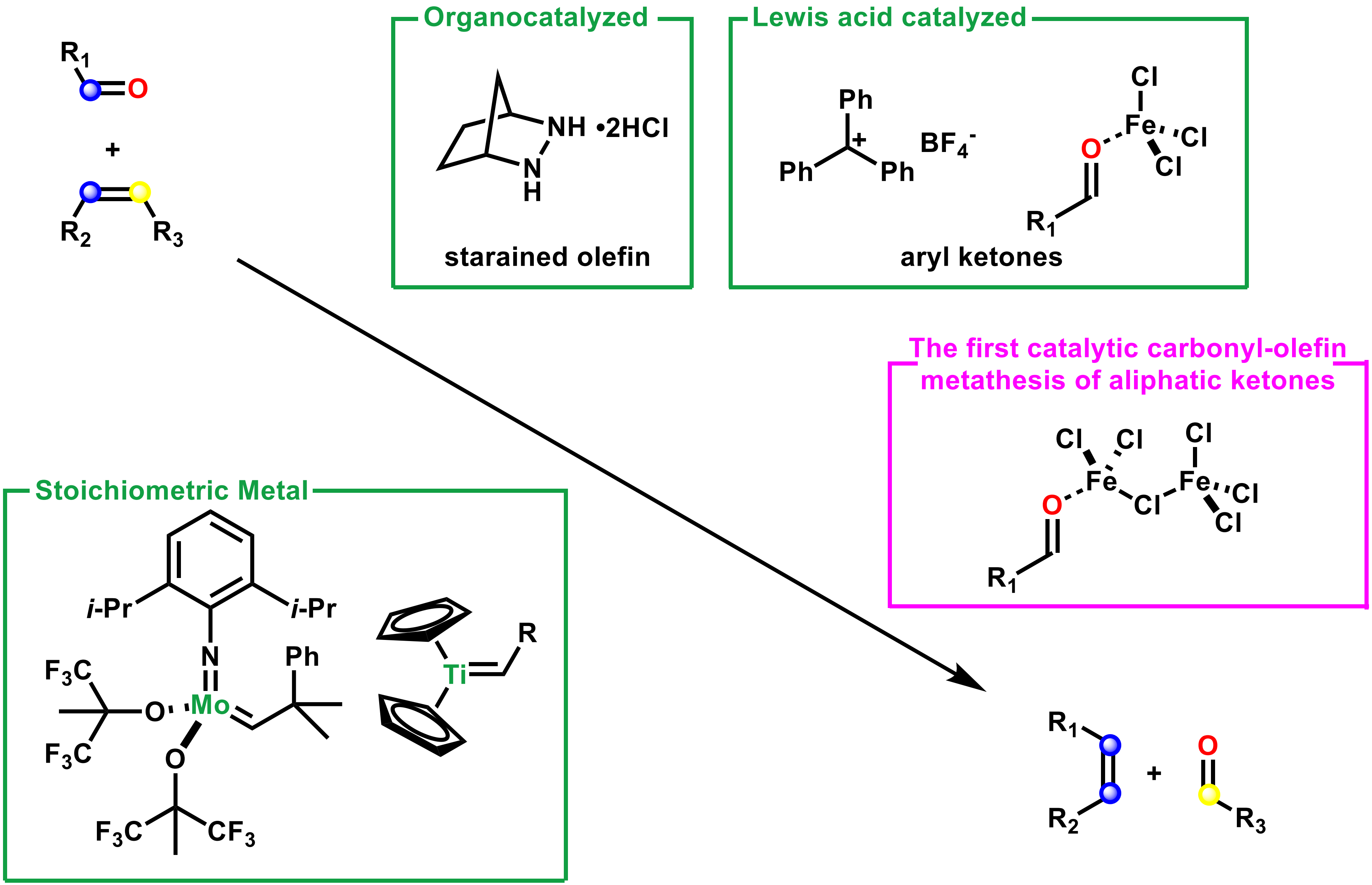
Summary



Organocatalyzed
NH •2HCl
N
H
starained olefin
Lewis acid catalyzed
Ph
+
Ph
Ph
BF4-
Cl
O
Fe
Cl
Cl
R1
aryl ketones
The first catalytic carbonyl-olefin metathesis of aliphatic ketones
Cl
Cl
Cl
Fe
Fe
O
Cl
Cl
Cl
R1
Stoichiometric Metal
i-Pr
i-Pr
N
Ph
F3C
O
Mo
F3C
O
F3C
CF3
Ti
R
R1
O
R2
R3

Appendix