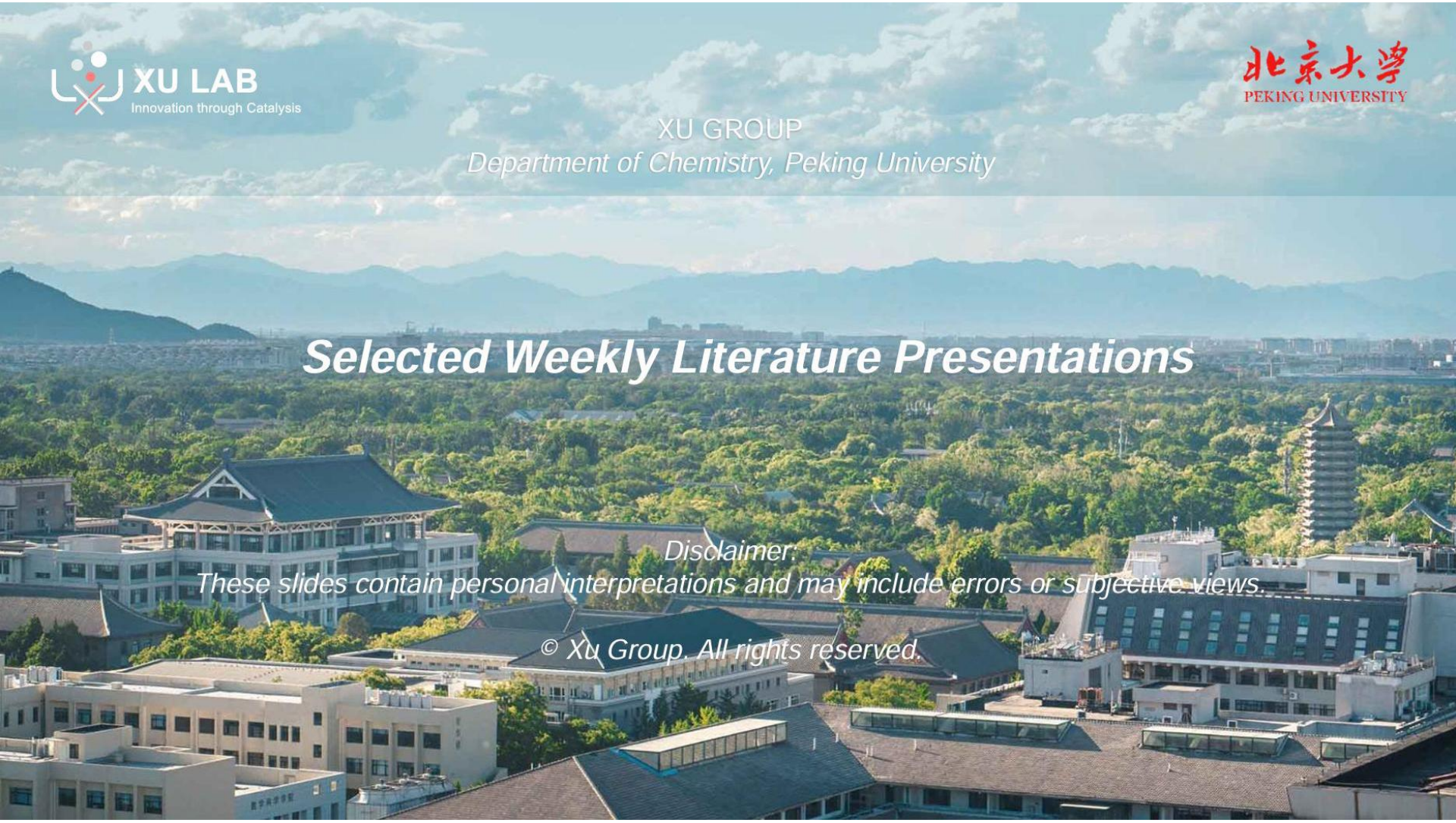


XU GROUP

Department of Chemistry, Peking University

Selected Weekly Literature Presentations

Disclaimer:

These slides contain personal interpretations and may include errors or subjective views.

Lewis Acid Catalyzed Carbonyl-Olefin Metathesis Reactions

He Peimiao

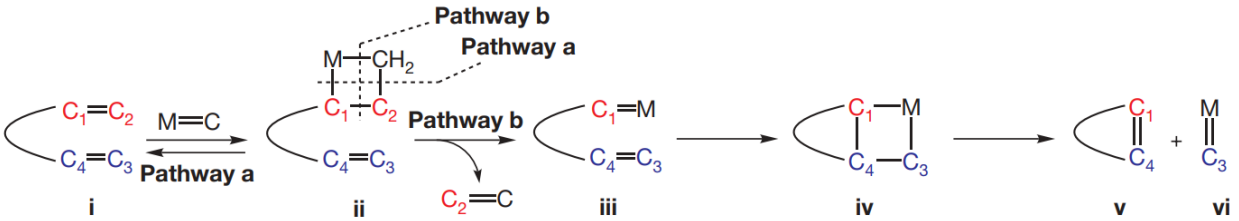
Collage of Chemistry and Molecular Engineering

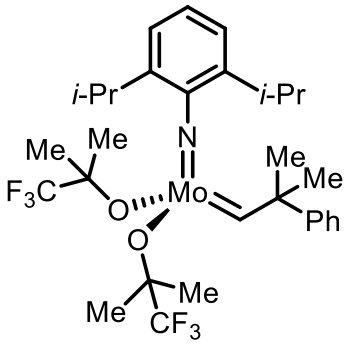
Outline

- Introduction
- Ring-Closing COM
- Other-Type COM
- Summary and Acknowledgement

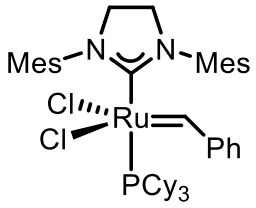
Introduction

- Olefin-Olefin Metathesis vs. Carbonyl-Olefin Metathesis

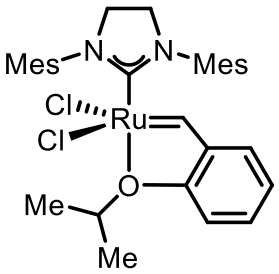




Schrock (1990)

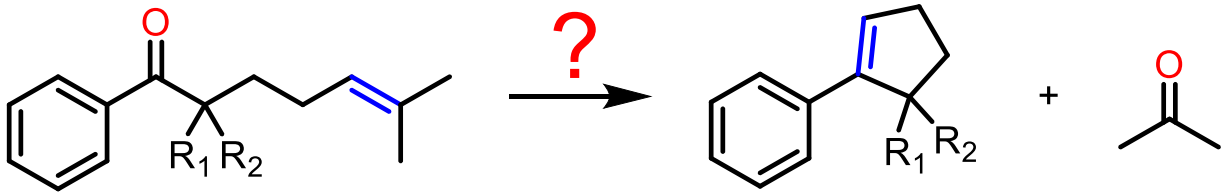


Grubbs (1999)



Hoveyda (2000)

- ✓ Cross Metathesis
- ✓ Ring-Closing Metathesis
- ✓ Ring-Opening Metathesis
- ✓ ROMP and ADMET



- Irreversible
- Lack of General Strategy

Hoveyda, A. H.; Zhugralin, A. R. *Nature*, **2007**, 450, 243–251

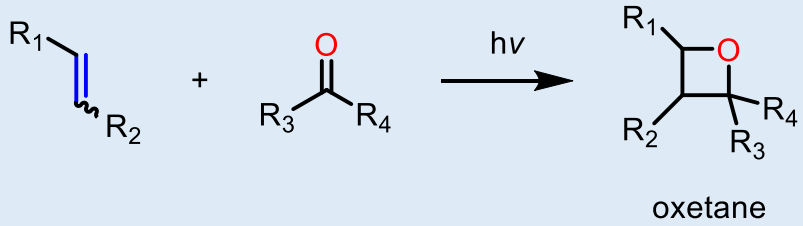
Schrock, R. R. *et al. J. Am. Chem. Soc.* **1990**, 112, 10, 3875–3886

Grubbs, R. H. *et al. Org. Lett.* **1999**, 1, 6, 953–956

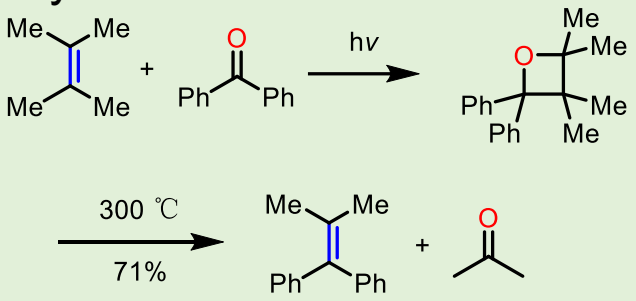
Hoveyda, A. H. *et al. J. Am. Chem. Soc.* **2000**, 122, 34, 8168–8179

Strategies Developed Earlier

■ Paternò−Büchi Reaction

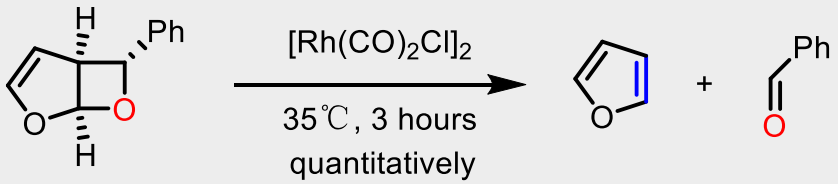


■ Pyrolysis

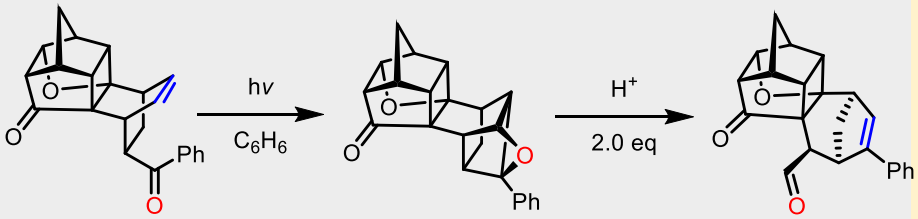


Jones, G. *et al. J. Chem. Soc., Chem. Commun.* **1973**, 374−375.

■ Acid Catalyzed Fragmentation

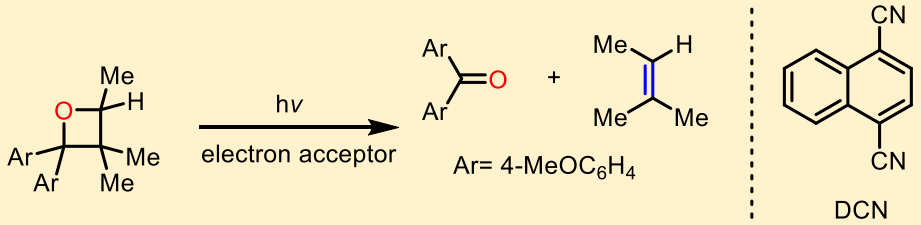


Adames, G. *et al. J. Chem. Soc., Chem. Commun.* **1972**, 491−492

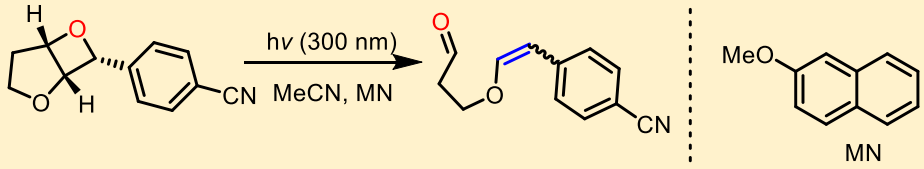


Kutateladze, A. G. *et al. J. Org. Chem.* **2011**, 76, 5, 1319–1332

■ Electron Transfer



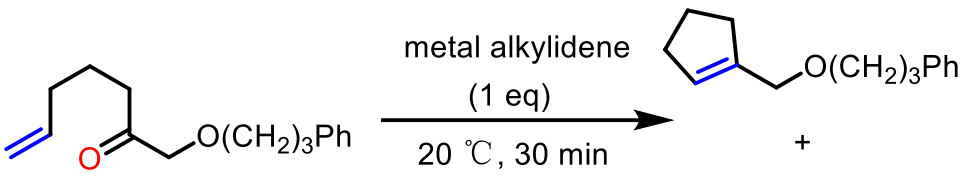
Shima, K. *et al. Bull. Chem. Soc. Jpn.* **1989**, 62, 96−101

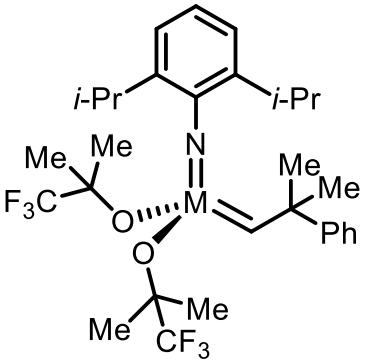


Griesbeck, A. G. *et al. Photochem. Photobiol. Sci.* **2006**, 5, 51−55.

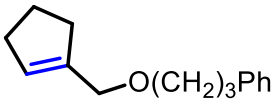
Strategies Developed Earlier

- Transition Metal Reagent

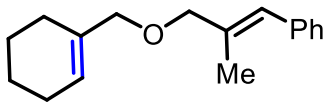




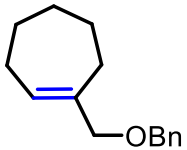
M=Mo or W



86%

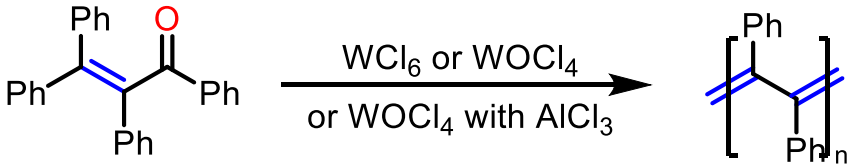


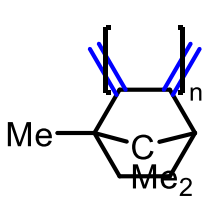
84%

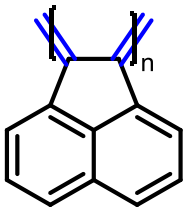


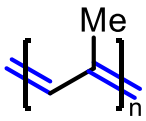
86%

- Polymerization







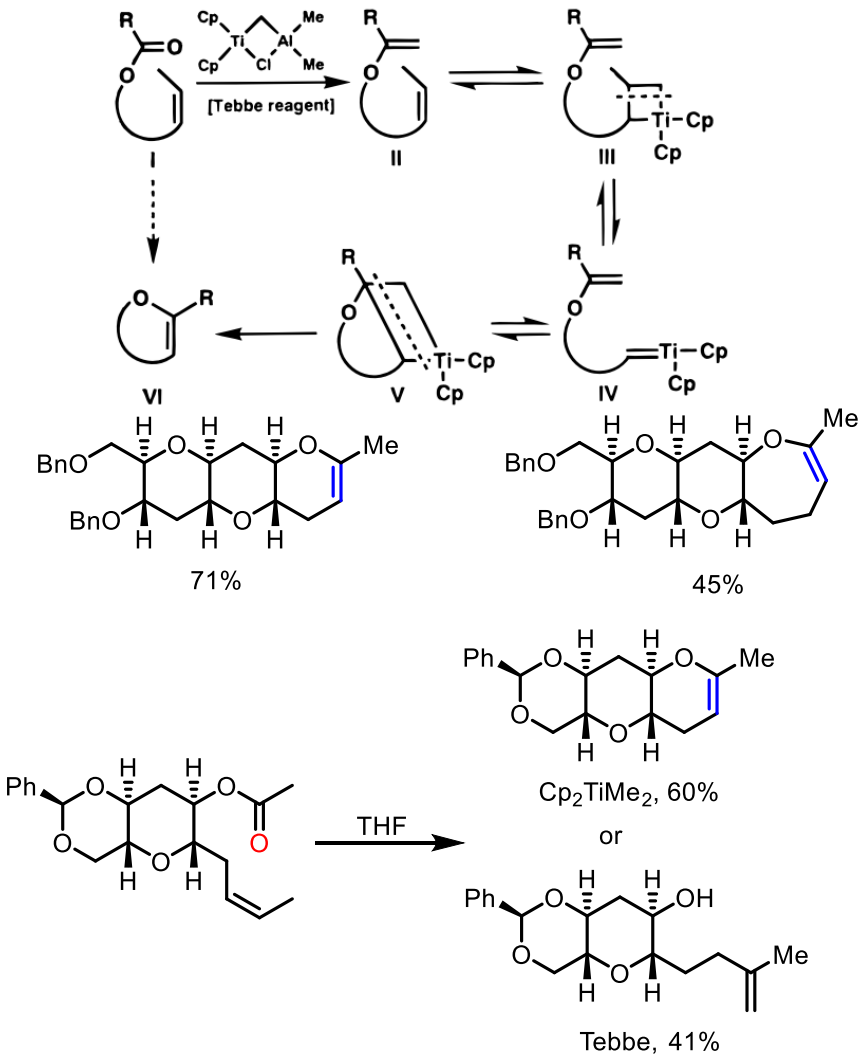


- Only Conjugated Monomers
- Step-Growth Polymerization
- No “Back-Biting-Reaction”

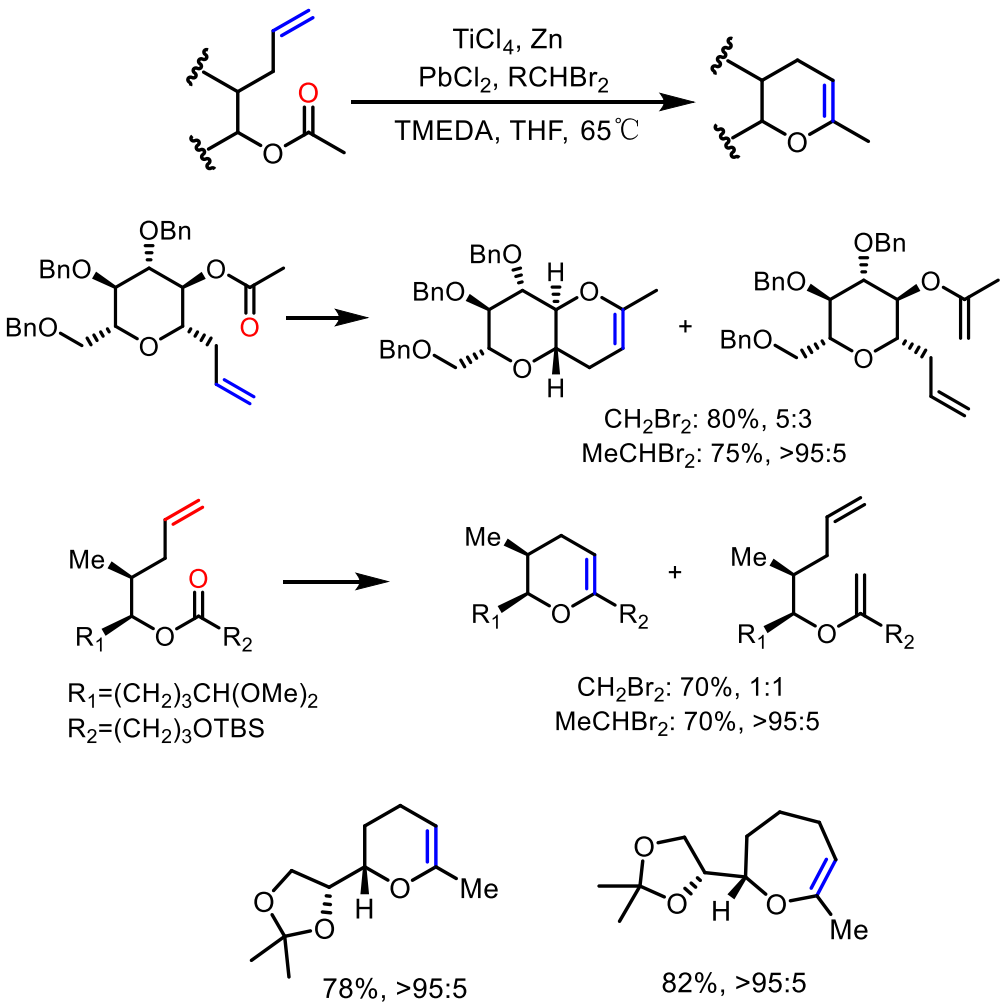
Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, 115, 9, 3800–3801 Jossifov, C.; Schopov, I. *Makromol. Chem.* **1991**, 192, 863-866

Titanium Reagent

- Tebbe Reagent (4 eq)



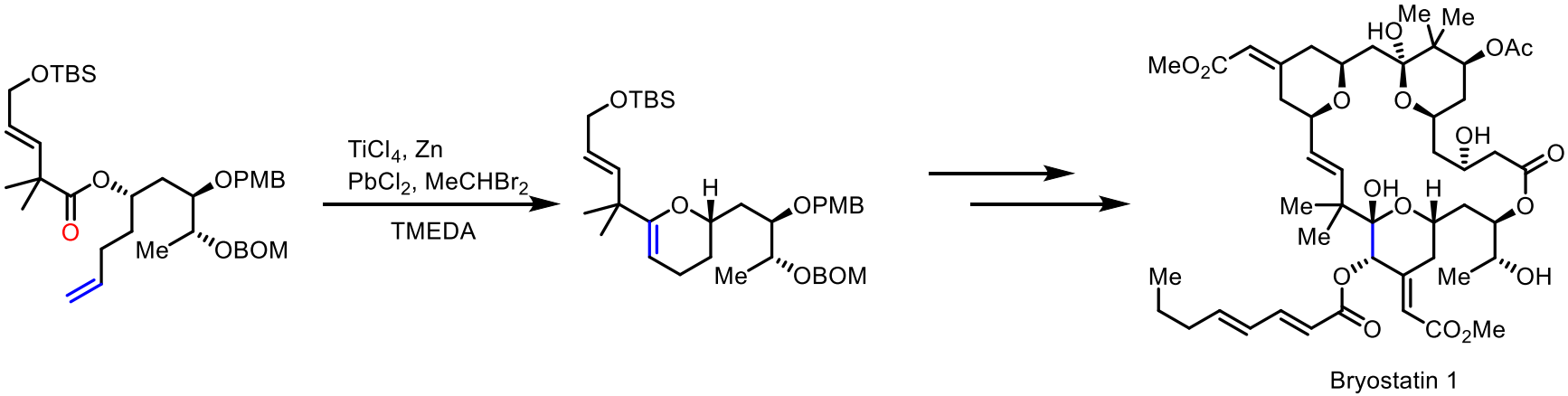
- Takai−Utimoto Condition



Nicolaou, K. C. *et al*. *J. Am. Chem. Soc.* **1996**, 118, 6, 1565–1566

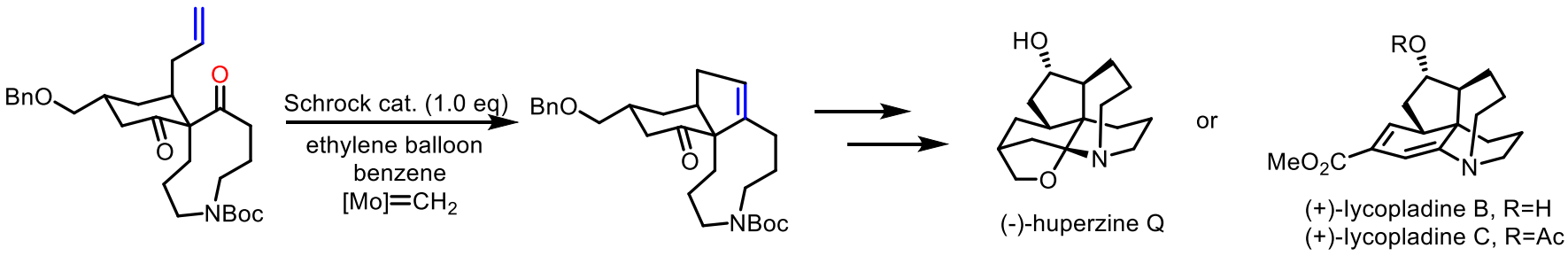
Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2007**, 129, 42, 12604–12605

Applications



Bryostatin 1

Keck, G. E.; Poudel, Y. B.; Cummins, T. J.; Rudra, A. Cocel, J. A. *J. Am. Chem. Soc.* **2011**, 133, 4, 744–747



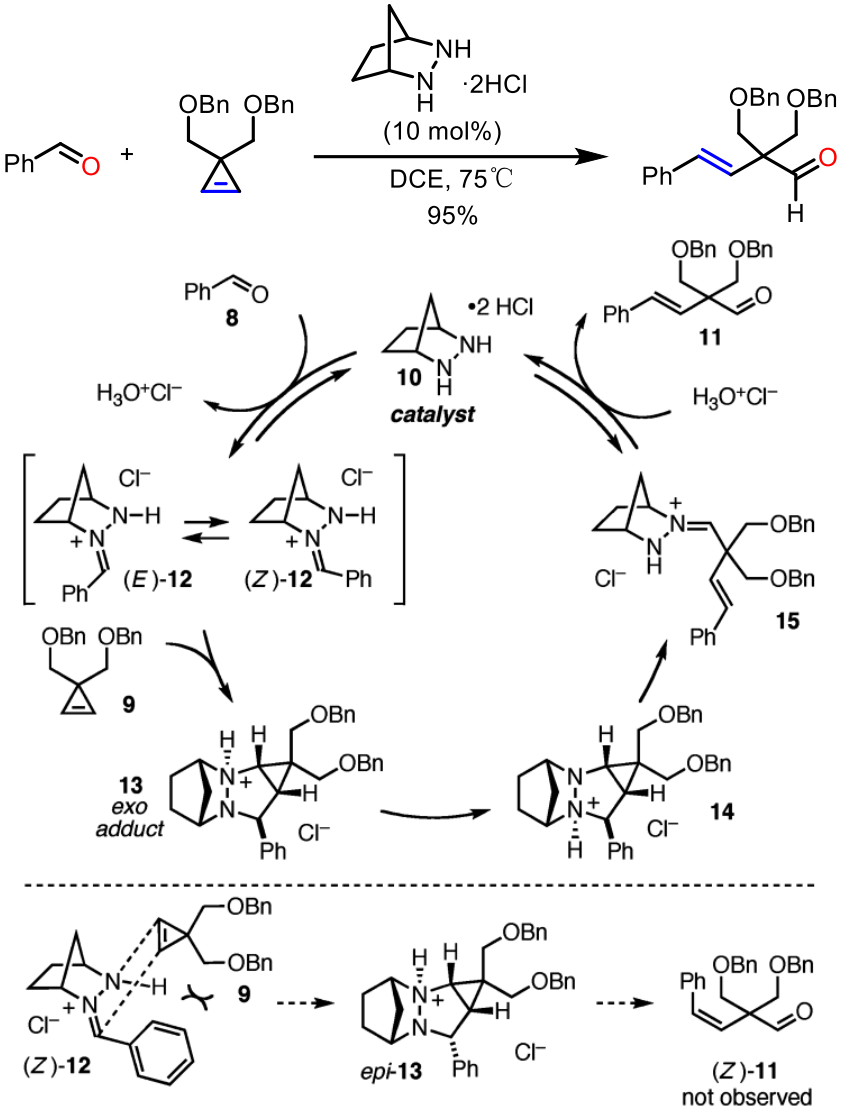
(-)-huperzine Q

(+)-lycopladine B, R=H
(+)-lycopladine C, R=Ac

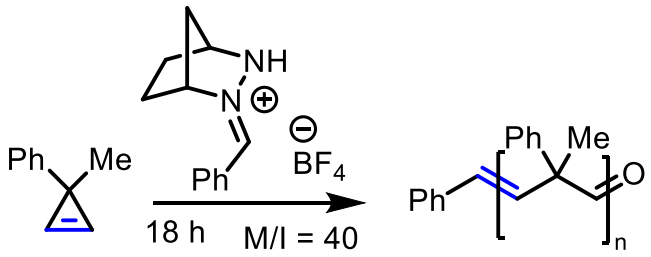
Hong, B.; Li, H.; Wu, J.; Zhang, J.; Lei, X. *Angew. Chem. Int. Ed.* **2015**, 54, 1011 –1015

Organocatalytic COM

■ Bicyclic Hydrazine



■ Chain Polymerization



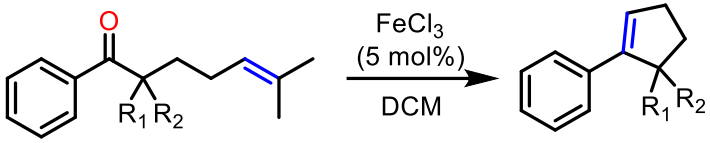
temp (ºC)	DP	M_n theo (kDa)	M_n exp (kDa)	$Đ$	yield (%)
60	46	5.2	6.1	1.5	25
70	50	5.2	6.6	1.3	23
80	35	5.2	4.6	1.3	27
90	25	5.2	3.4	1.3	29
100	29	5.2	3.9	1.3	18

Lambert, T. H. *et al. J. Am. Chem. Soc.* **2012**, 134, 45, 18581–18584

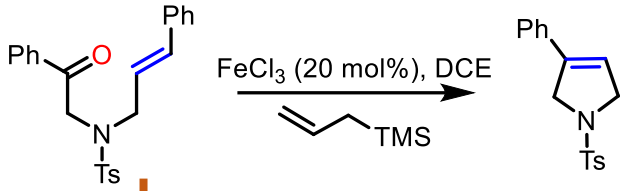
Lamber, T. H. *et al. Angew. Chem. Int. Ed.* **2022**, 134, e202203344

Time Line of Carbonyl-Olefin Metathesis

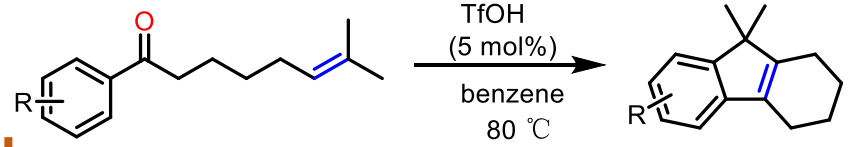
Corinna S. Schindler



Zhiping Li



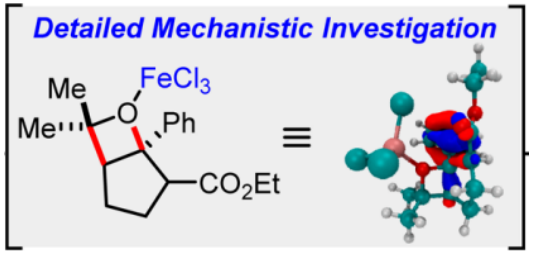
Corinna S. Schindler



Corinna S. Schindler

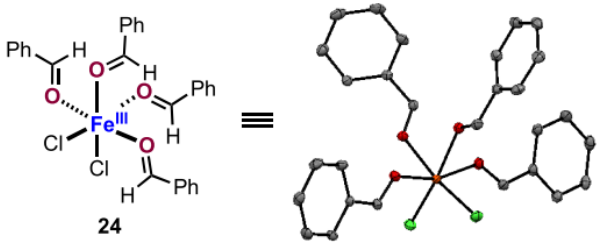
2016 — 2017 — 2018 — 2019 — 2020 — 2021

Corinna S. Schindler



James J. Devery:

Solution behavior of catalyst



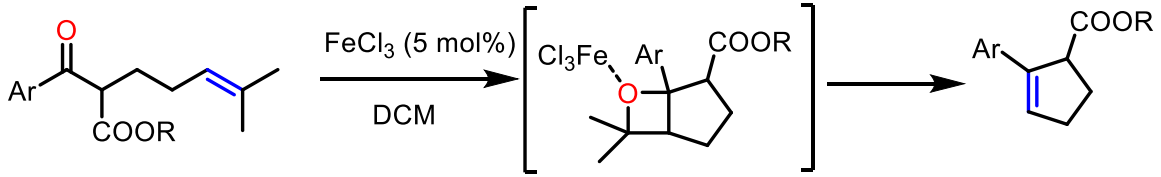
Paul M. Zimmerman and James J. Devery:
Combination of theoretical model and experimental evidence of the solution behavior

Outline

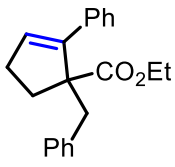
- Introduction
- Ring-Closing COM
- Other-Type COM
- Summary and Acknowledgement

$FeCl_3$ Catalyzed Ring-Closing COM

Reaction Model



Substrate Scope



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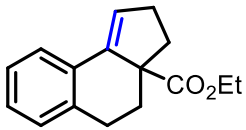

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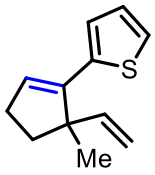

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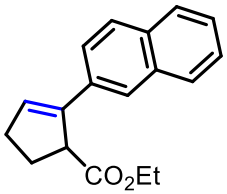

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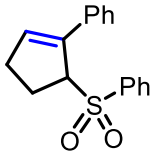

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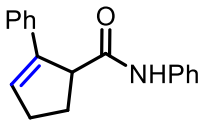

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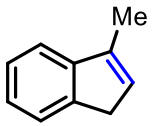

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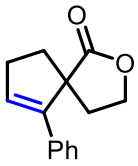

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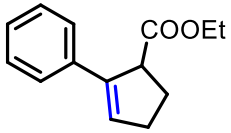
Ar Group



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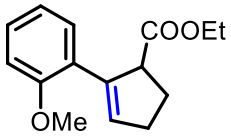

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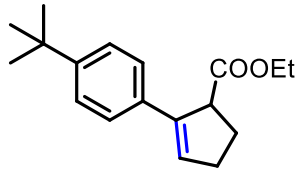

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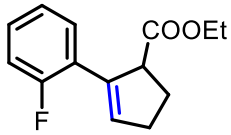

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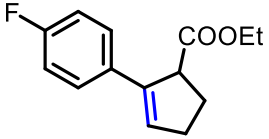
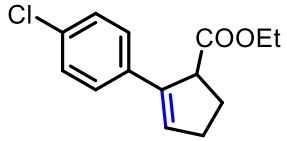


80%



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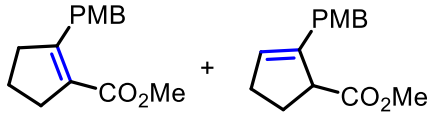


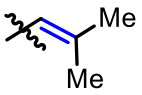
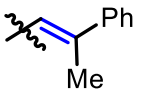
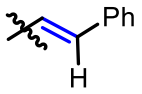
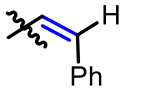
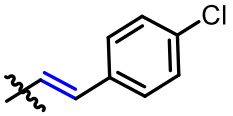
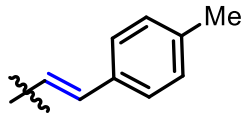
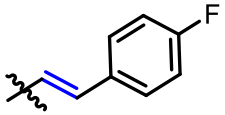
1:2, 99% yield

- ✓ Low catalyst loading and high yield
  - Only aromatic ketone
- ✓ Tolerate both electron rich and poor Ar
  - Mainly five-membered ring

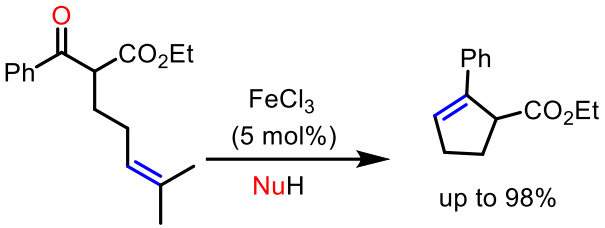
Ludwig, J. R.; Zimmerman, P. M.; Gianino, J. B.; Schindler, C. S. *Nature*, **2016** 533, 374–379

Initial Mechanism Study

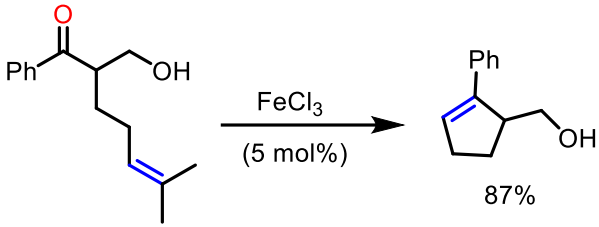
■ Alkene Evaluation

Alkene	Yield
	99%
	49%
	60%
	49%
	60%
	62%
	70%

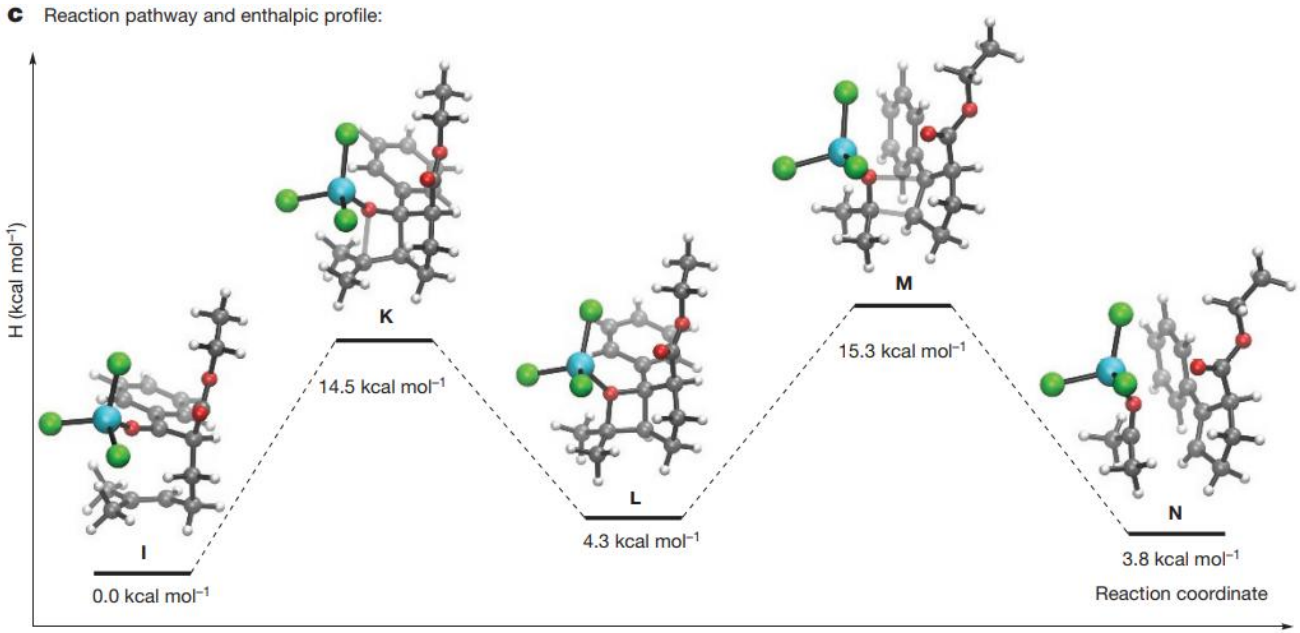
■ Mechanistic Probes



NuH = MeOH, *i*-PrOH, AcOH, benzoic acid



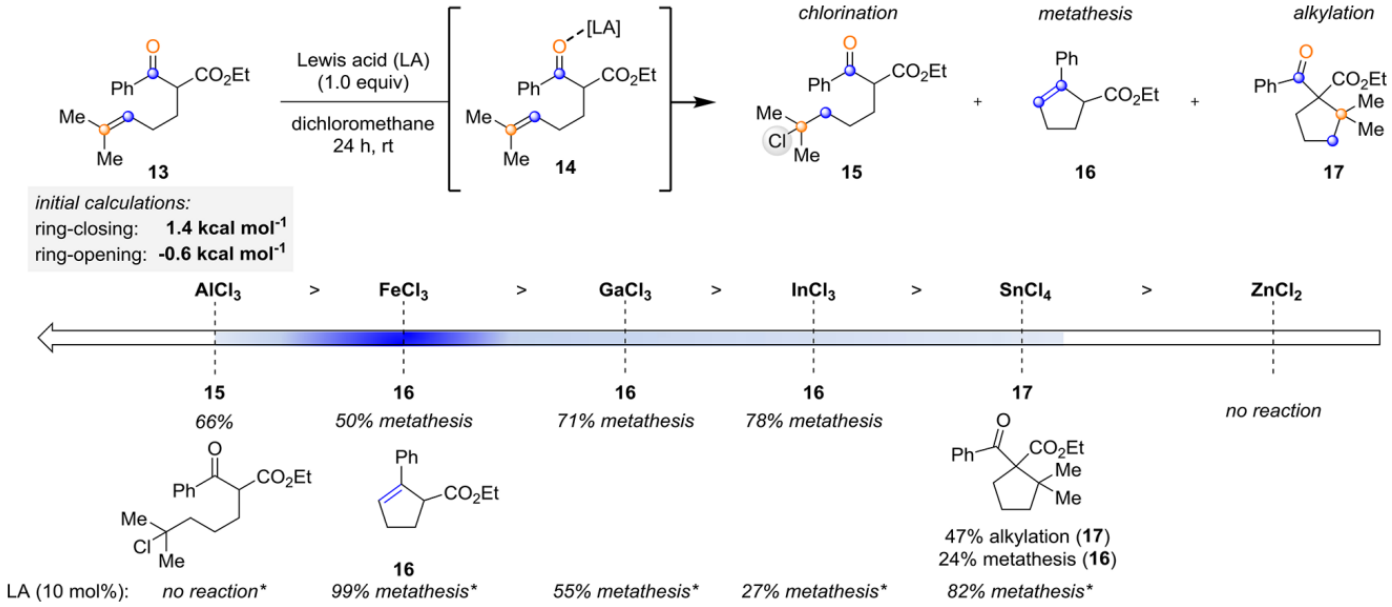
■ Concerted yet Asynchronous Cyclization



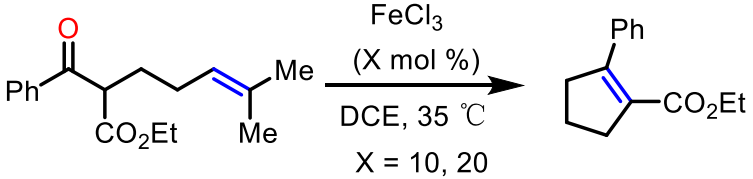
Through the ZStruct Method

Detailed Mechanism Investigation

■ Evaluation of Lewis Acids



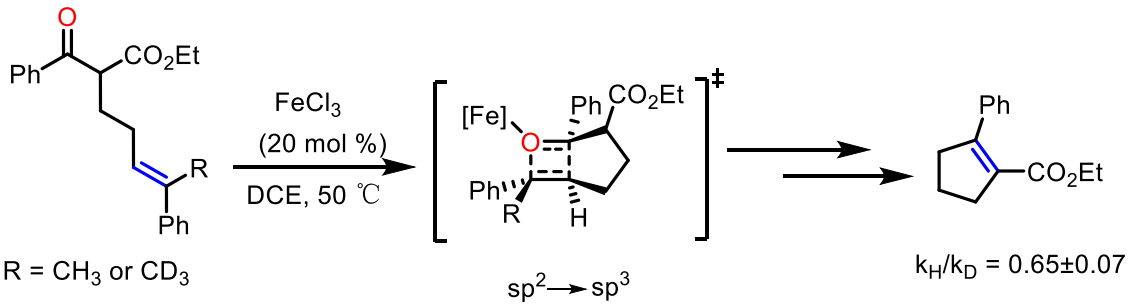
■ Rate Order Determination



Rate order of $FeCl_3$ = 1.1±0.2

Substrate: Zere Order

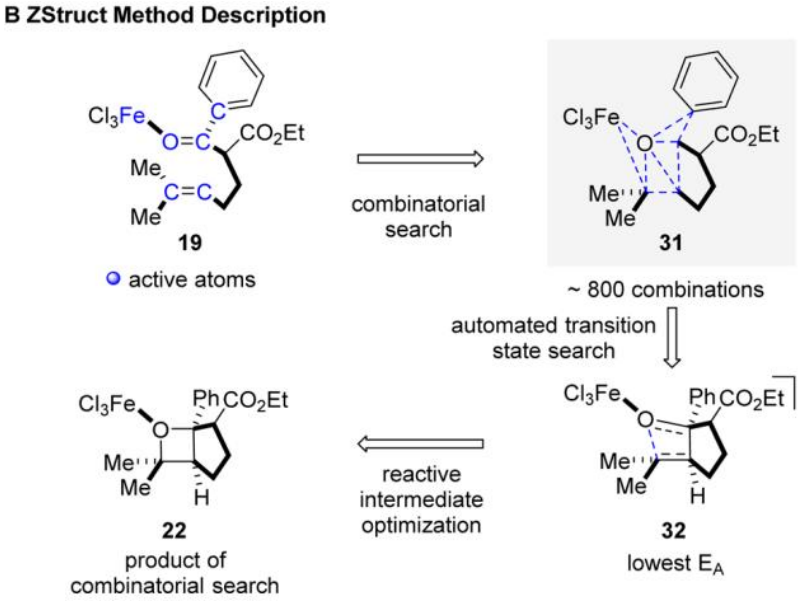
■ KIE and RDS

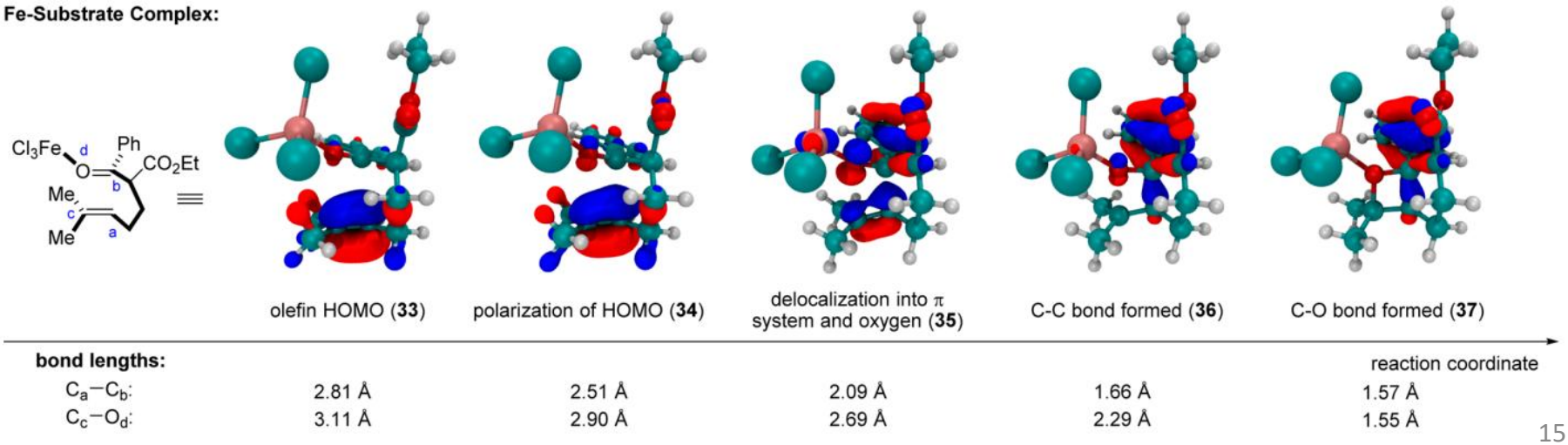


Ludwig, L. R.; Phan, S.; McAtee, C. C.; Zimmerman, P. M.; Devery, J. J.; Schindler, C. S. *J. Am. Chem. Soc.* **2017**, 139, 31, 10832–10842

Oxetane Formation

- Concerted yet Asynchronous
- Electrons Delocalization
- Consistent with the W-H Rules

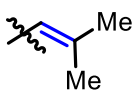
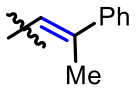
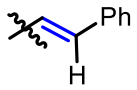
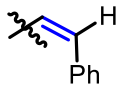
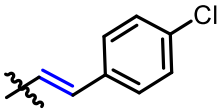
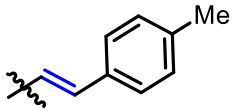
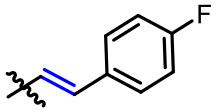
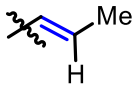




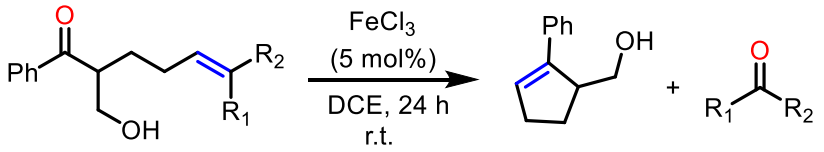
Ludwig, L. R.; Phan, S.; McAtee, C. C.; Zimmerman, P. M.; Devery, J. J.; Schindler, C. S. *J. Am. Chem. Soc.* **2017**, 139, 31, 10832–10842

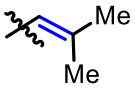
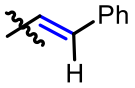
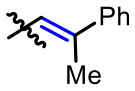
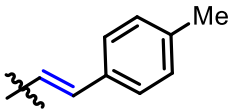
Oxetane Fragmentation

- Substrate-Dependent Fashion

Alkene	Result
	No stationary points on PES Concerted
	Stepwise
	Stepwise
	Stepwise
	Stepwise
	Stepwise
	Stepwise
	Stepwise

- Intramolecular Trapping Experiments

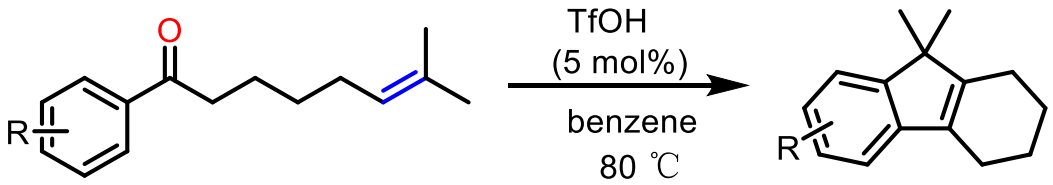


Substrates	Yield	Conv.
	87%	100%
	35%	78%
	16%	81%
	29%	86%

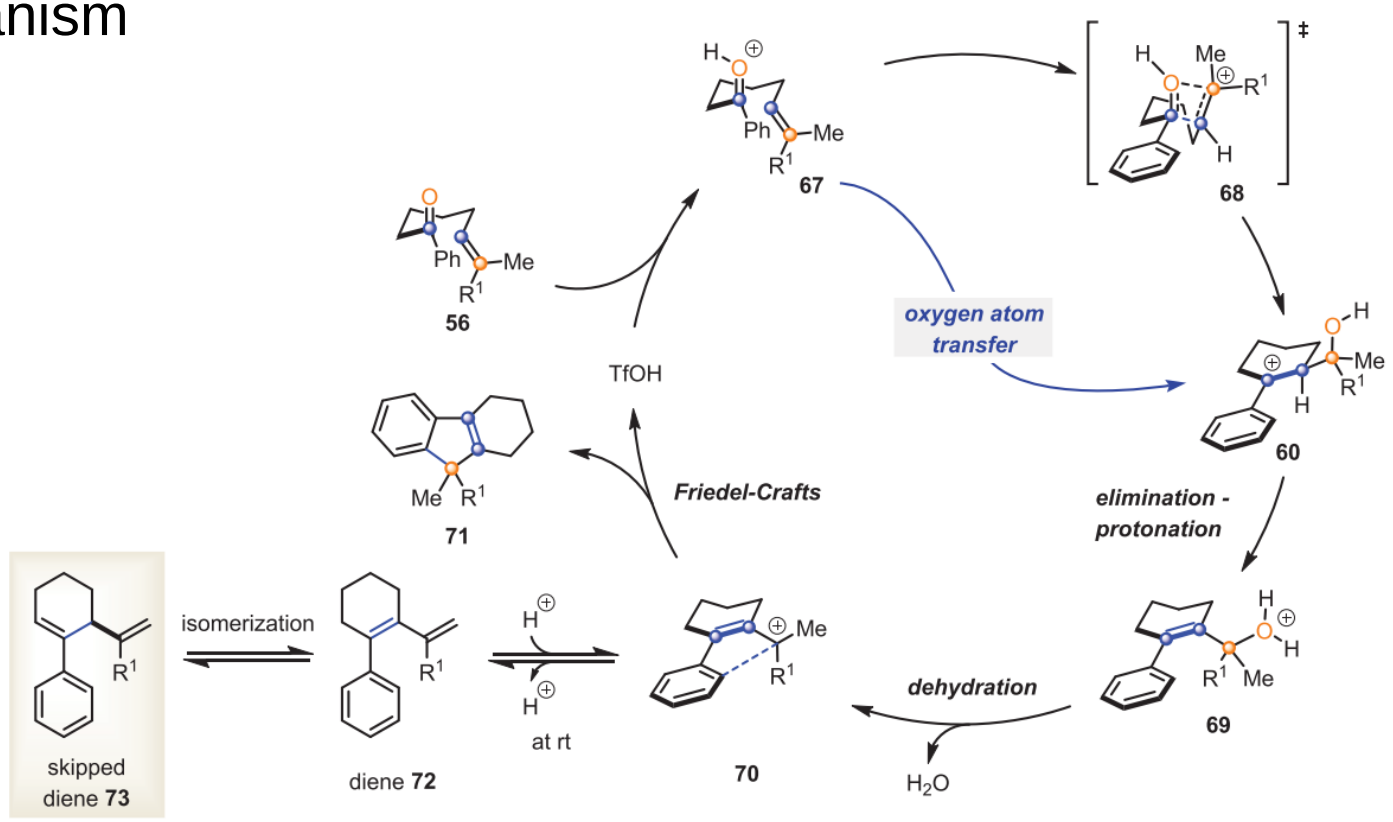
Complex Mixture of Products

Schindler, C. S. *et al. J. Am. Chem. Soc.* **2017**, 139, 31, 10832–10842

Interrupted COM



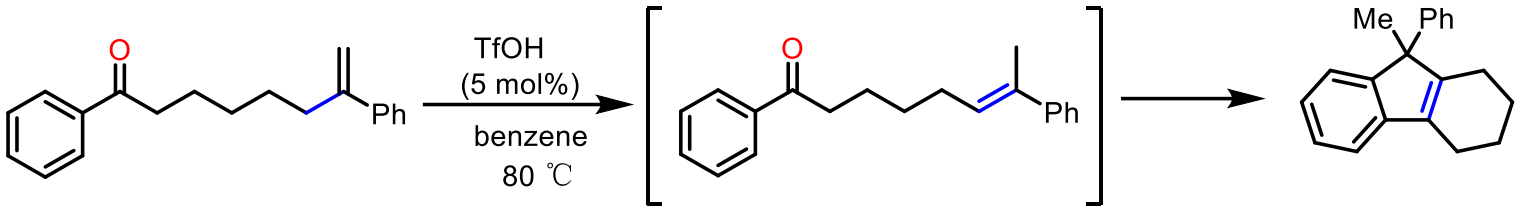
■ Mechanism



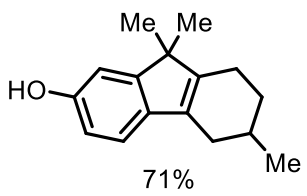
Schindler, C. S. *et al. Science*, **2018**, 361, 1363–1369

Interrupted COM

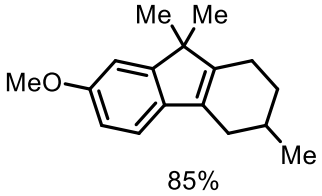
- *in situ* Isomerization



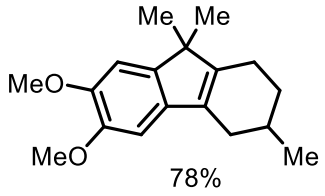
- Selected Examples



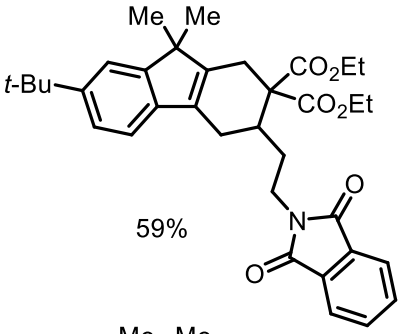
71%



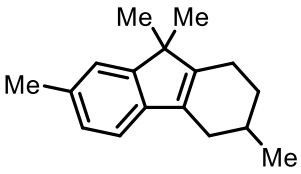
85%



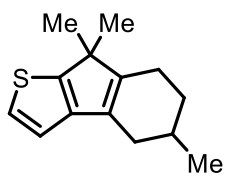
78%



59%



92%



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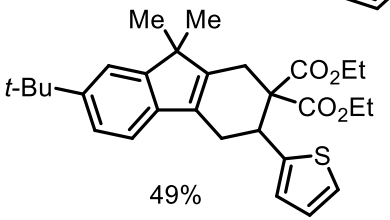
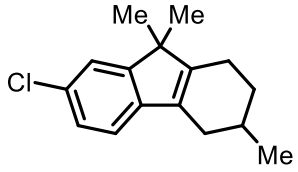
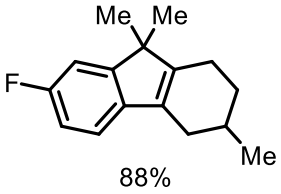


49%



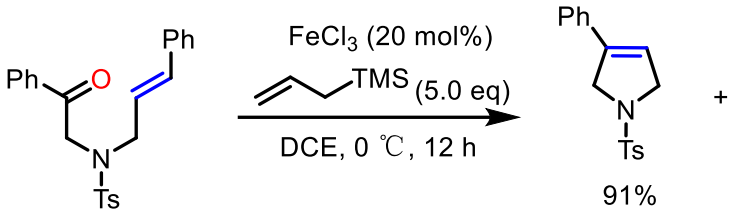
66%



88%

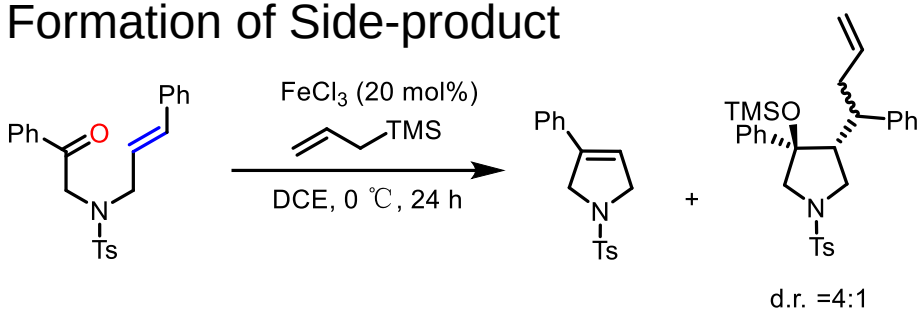
Synthesis of Tetrahydropyridine

■ Additive



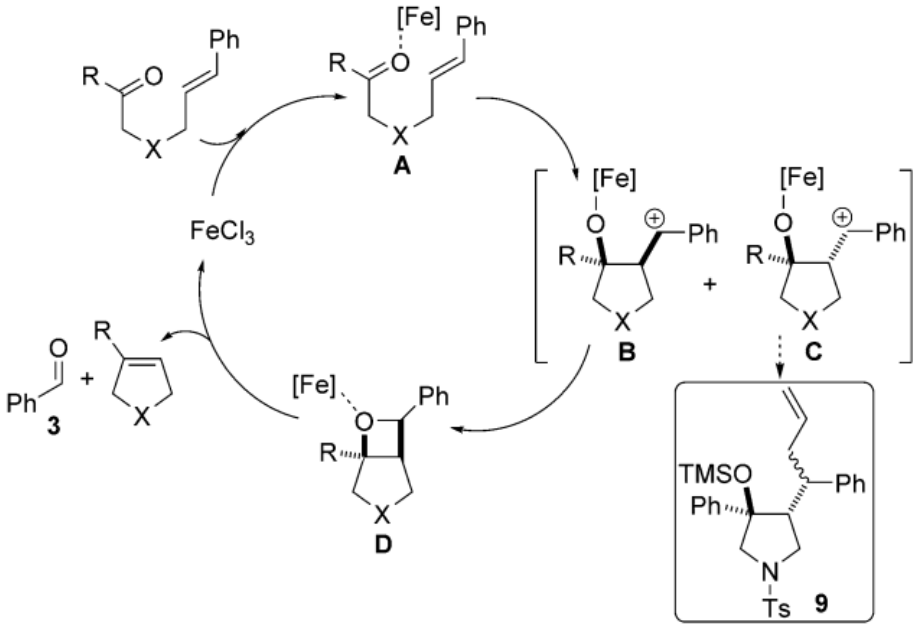
$FeCl_3$ (mol%)	Additive	Yield
50	none	ND
50	TMS	95%
20	TES	11%
20	$SiMe_2Ph$	13%
20	TBS	<5%
20	Ph TES	<5%
20	Ph TMS	10%

■ Formation of Side-product



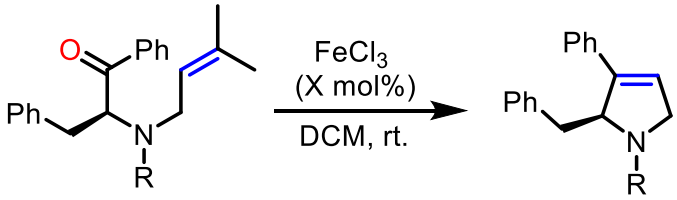
d.r. =4:1

■ Mechanism

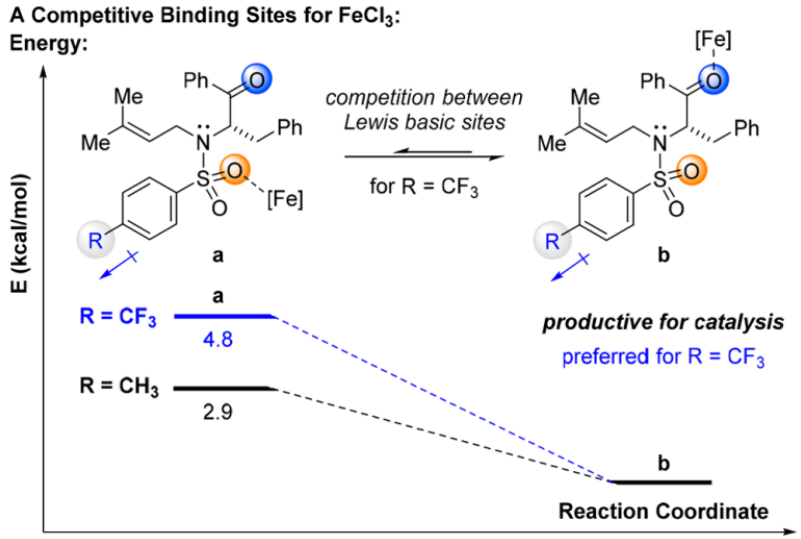


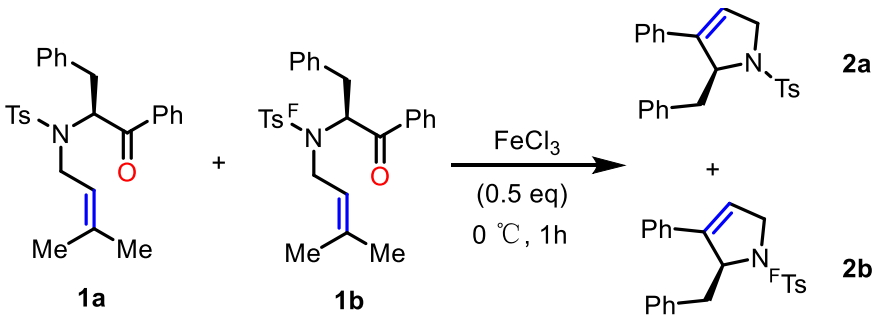
Ma, L.; Li, W.; Xi, H.; Bai, X.; Ma, E.; Yan, X.; Li, Z. *Angew. Chem. Int. Ed.* **2016**, 55, 10410 –10413

Synthesis of Tetrahydropyridine



X mol%	R	Yield	Conv.
20	Ts	19%	19%
30	Ts	24%	24%
40	Ts	53%	91%
50	Ts	72%	100%
50	^{Cl}Ts	96%	100%
50	^{F}Ts	99%	100%
30	^{F}Ts	96%	100%
20	^{F}Ts	90%	100%
5	^{F}Ts	80%	100%

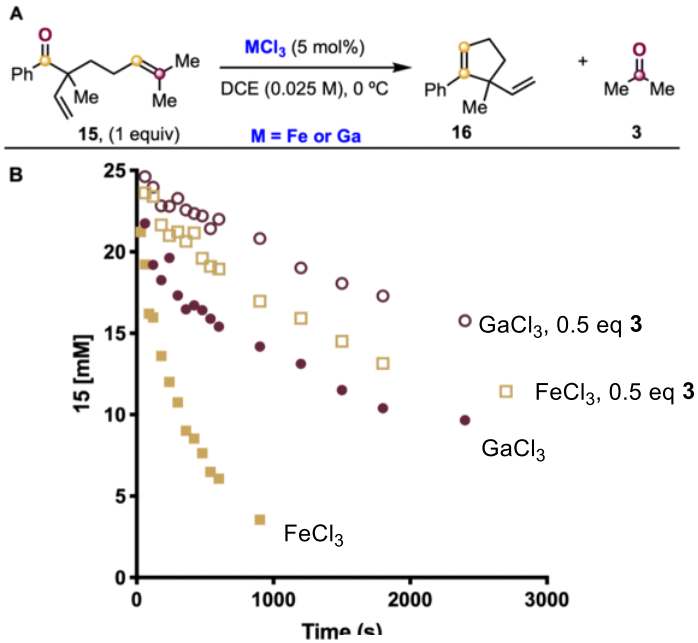




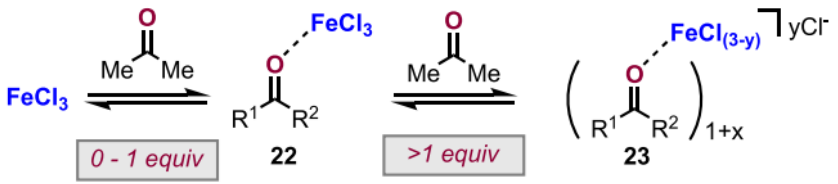
1a (eq)	**1b** (eq)	**2a**	**2b**
0	1	-	83%
0.3	1	49%	76%
1	1	56%	53%
1	0	66%	-

Schindler, C. S. *et al. ACS Catal.* **2018**, 8, 3, 2006–2011

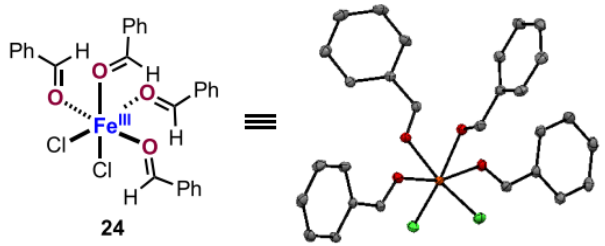
Catalyst Behavior of $FeCl_3$



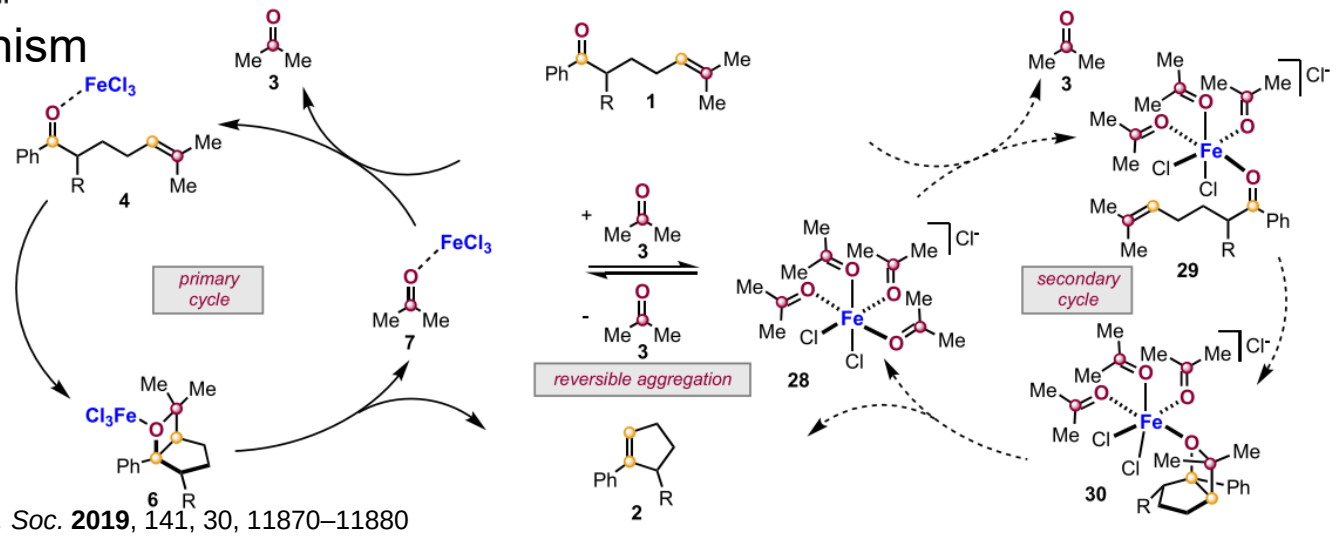
- Titration observed by IR and absorbance



- Crystal Structure (with $[FeCl_4]^-$ Counter-ion)

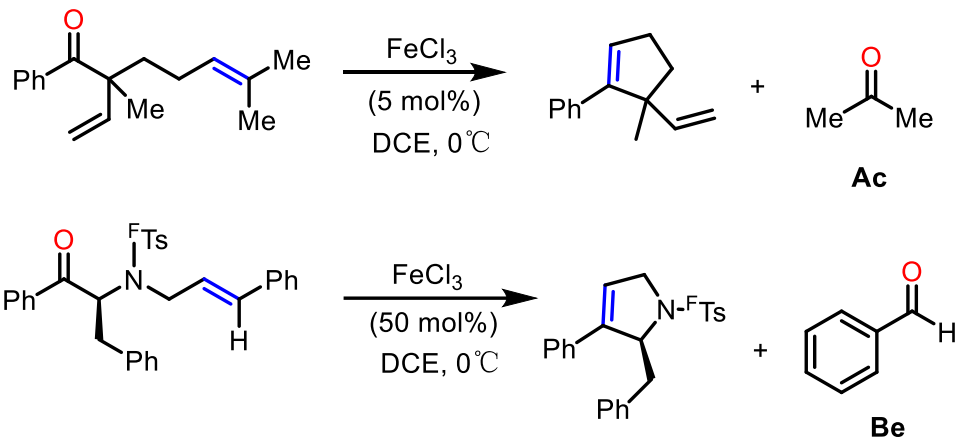


- Final Mechanism



Devery, J. J. *et al. J. Am. Chem. Soc.* **2019**, 141, 30, 11870–11880

Further Research



$3\mathbf{Ac} + FeCl_3\mathbf{Ac} \rightleftharpoons [FeCl_2\mathbf{Ac}_4]Cl$ ΔG=9.8 kcal/mol

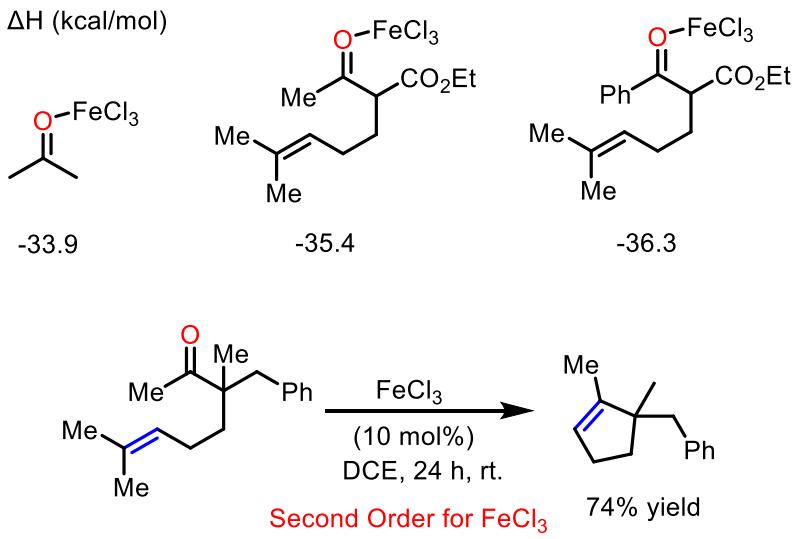
(active) (inactive)

$3\mathbf{Be} + FeCl_3\mathbf{Be} \rightleftharpoons [FeCl_2\mathbf{Be}_4]Cl$ ΔG=5.8 kcal/mol

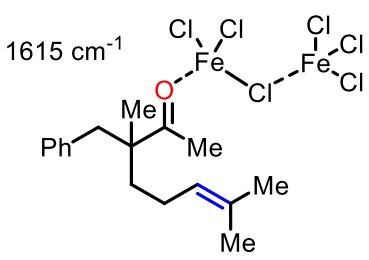
- Better stabilize the charge on the Fe center
- Distribution of charge across the four aromatic rings

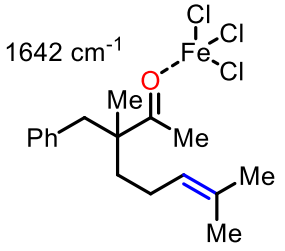
Malakar, T.; Hanson, C. S.; Devery, J. J.; Zimmerman, P. M. *ACS Catal.* **2021**, 11, 8, 4381–4394

Aliphatic Ketones

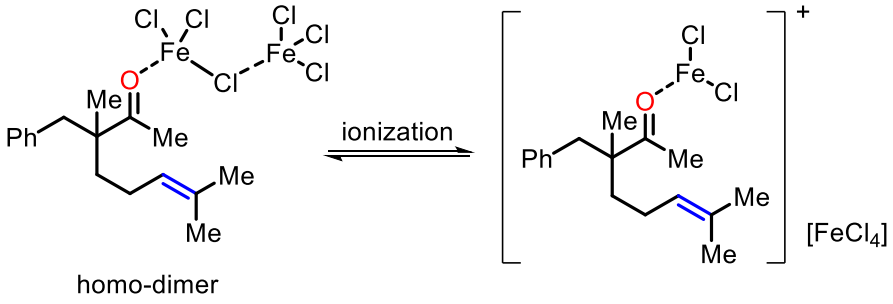


- Absence of $[FeCl_4]^-$ by Raman Spectra and EPR
- IR Result

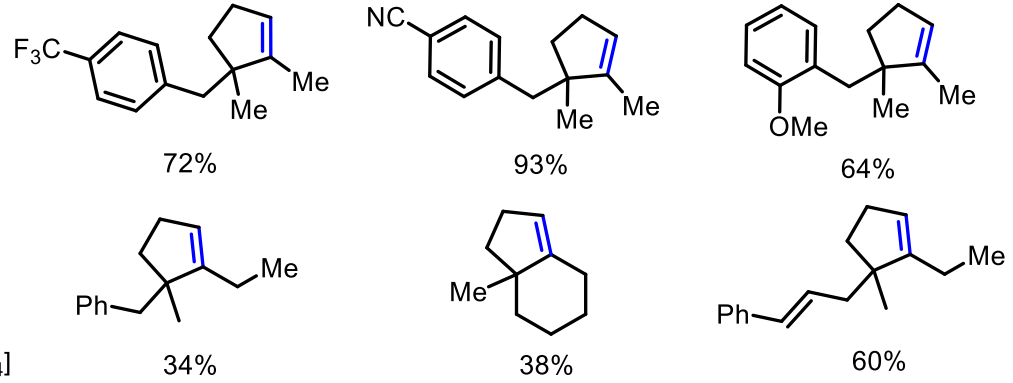




- Possible Intermediate

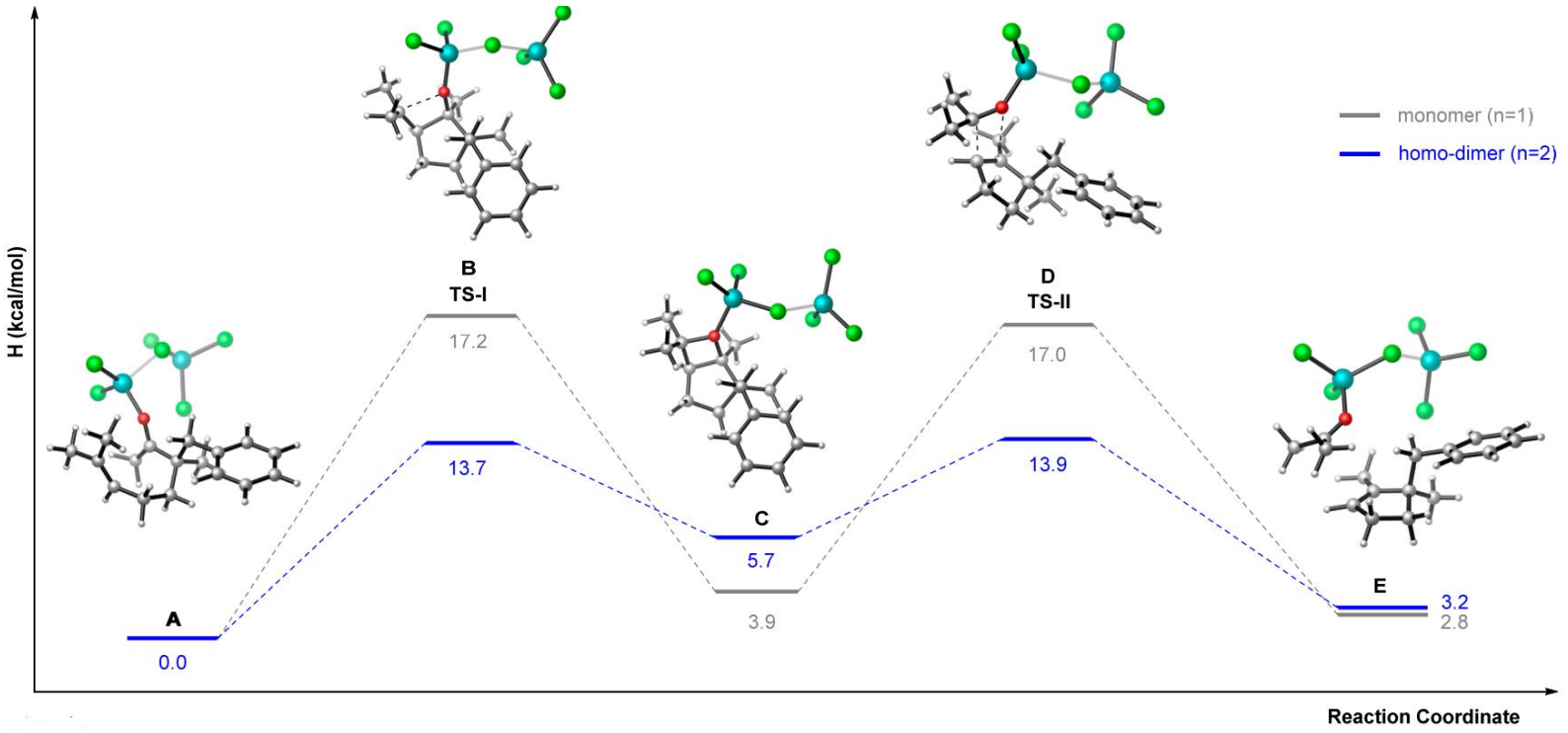


- Select Example



Schindler, C. S. *et al. J. Am. Chem. Soc.* **2019**, 141, 4, 1690–1700

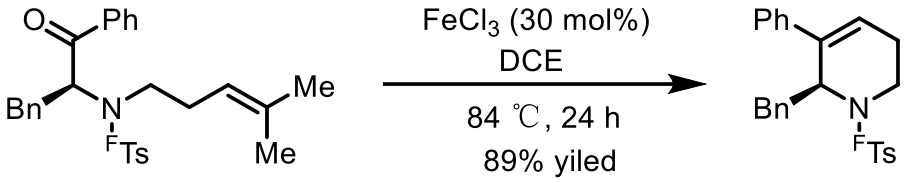
Aliphatic Ketones



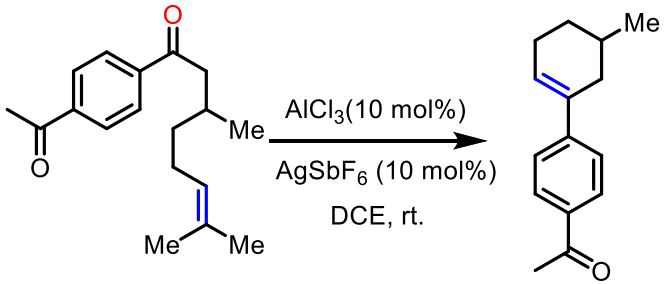
Schindler, C. S. *et al. J. Am. Chem. Soc.* **2019**, 141, 4, 1690–1700

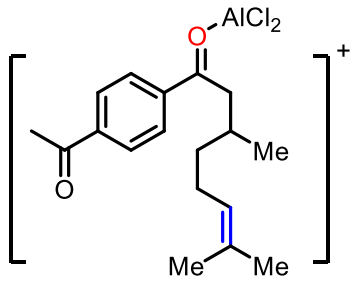
Formation of Six-Membered Ring

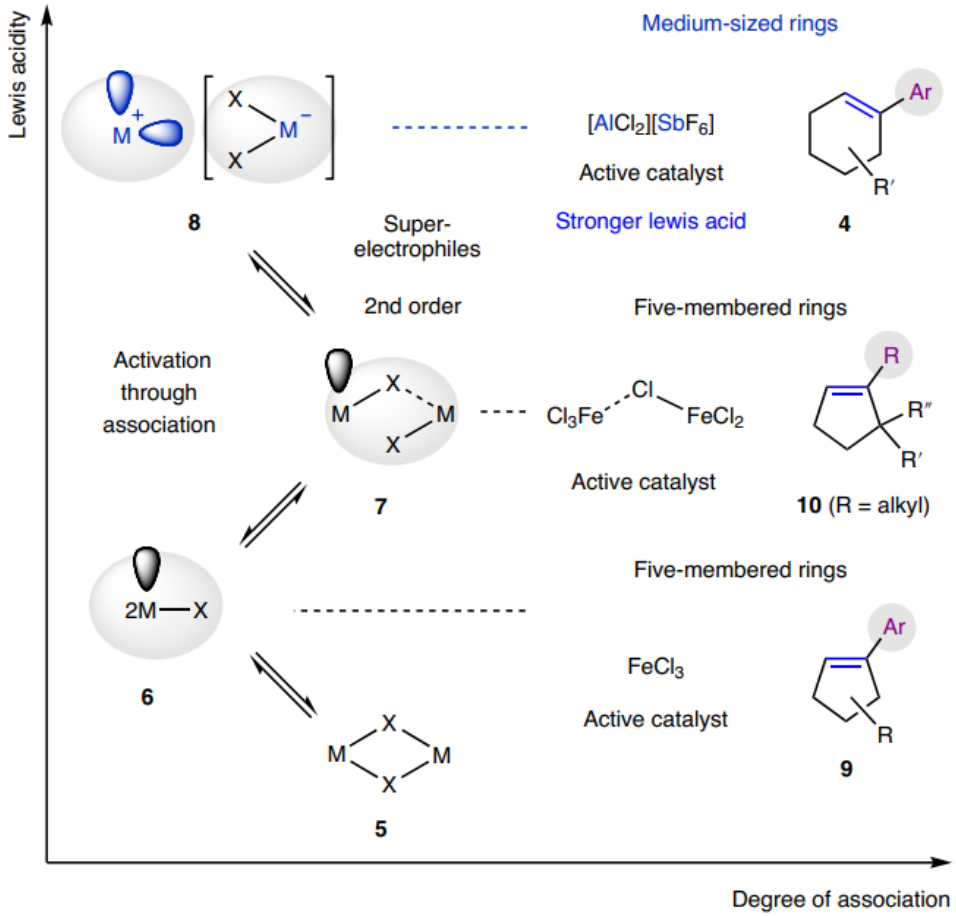
- Tetrahydropyridine



- Cyclohexenes





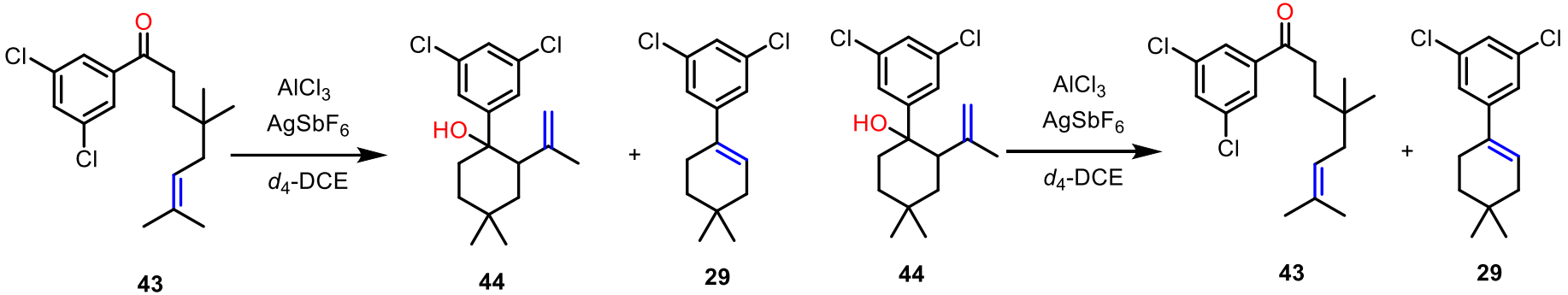


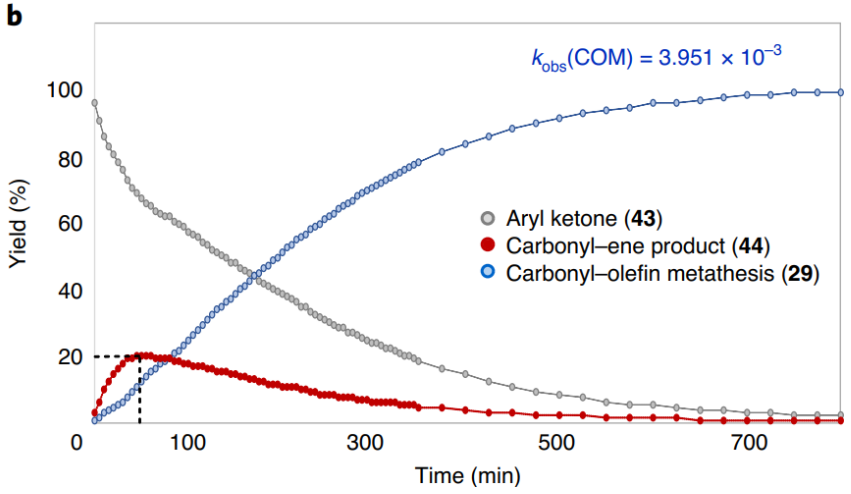
Schindler, C. S. *et al. Org. Lett.* **2020**, 22, 7, 2844–2848

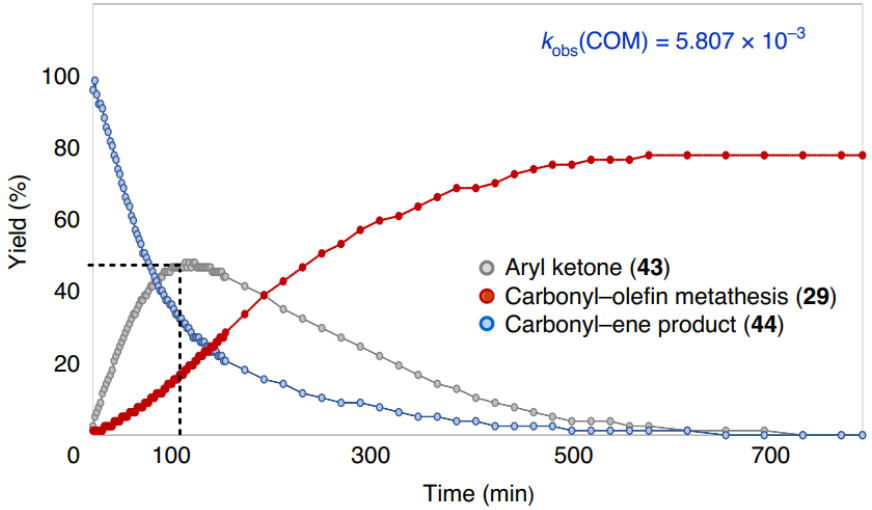
Schindler, C. S. *et al*. *Nat Catal,* **2020**, **3**, 787–796

Mechanistic Investigations

- Monitored by NMR analysis





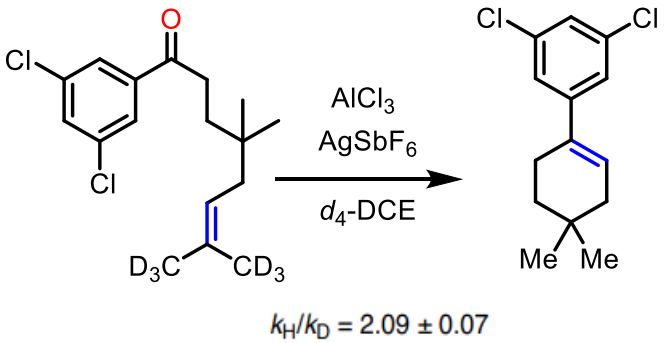


✓ Fast Equilibrium Between **43** and **44**

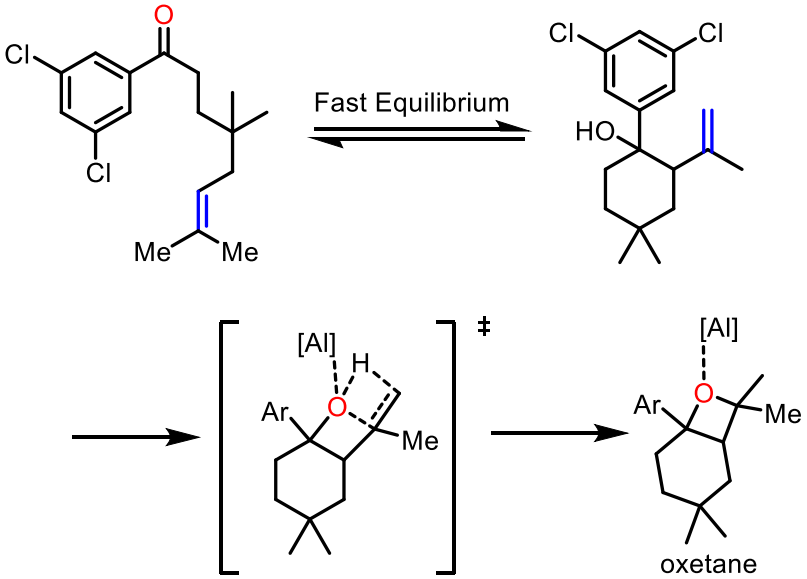
Schindler, C. S. *et al*. *Nat Catal,* **2020**, **3**, 787–796

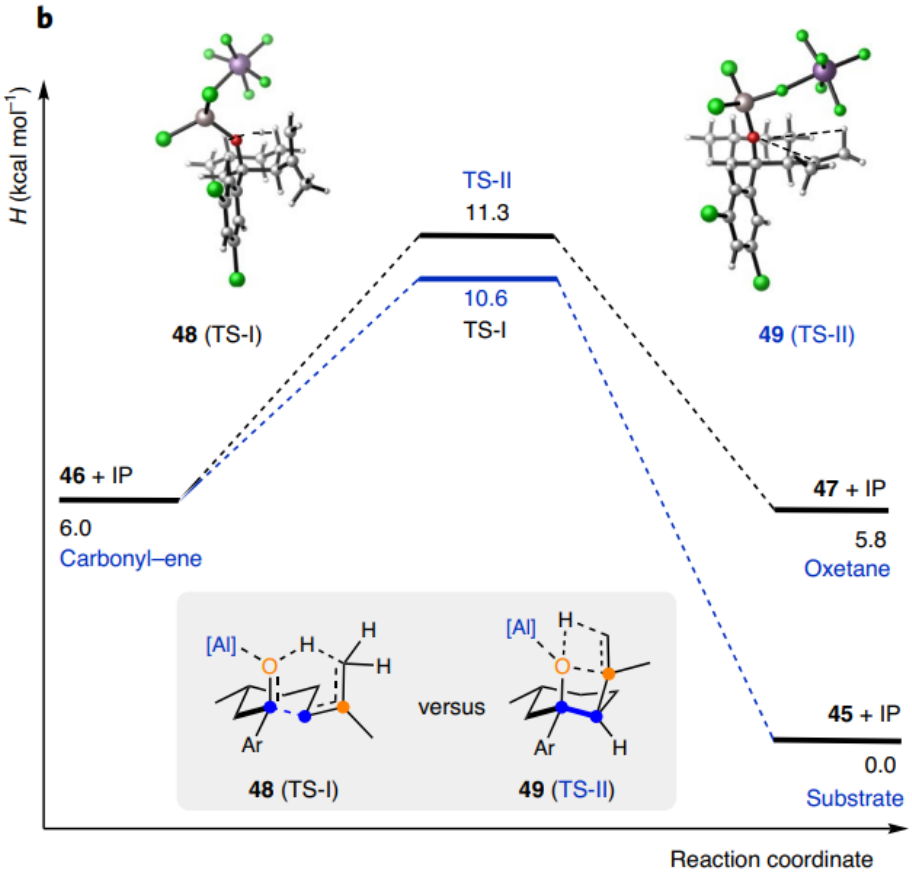
Mechanistic Investigations

- Kinetic Isotope Effect



- Proposed Mechanism

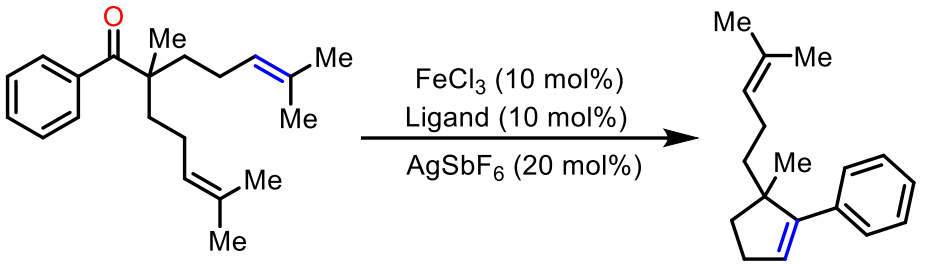


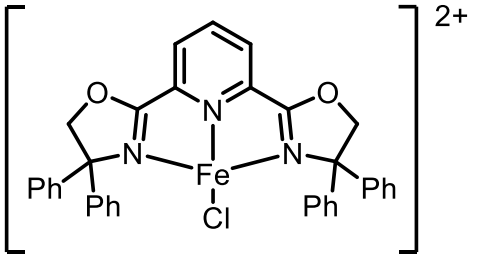


Schindler, C. S. *et al*. *Nat Catal,* **2020**, **3**, 787–796

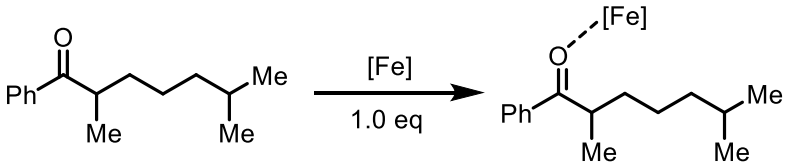
Tuning Lewis Acidity by Ligand

- Unpublished!



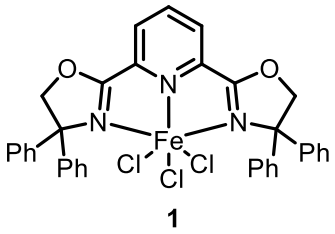


- Relative Lewis Acidity



LA	wave number (cm^{-1})
none	1681
1	1644
2	1615
$FeCl_3$	1558
3	1497
$FeCl_3$ dimer	1494
4	1471
$[FeCl_2][SbF_6]$	1463

Increasing Lewis Acidity



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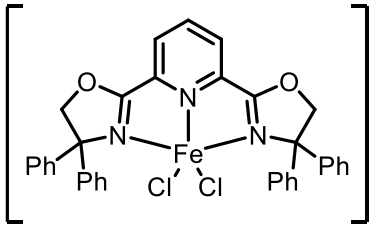

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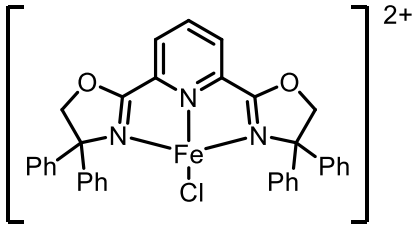

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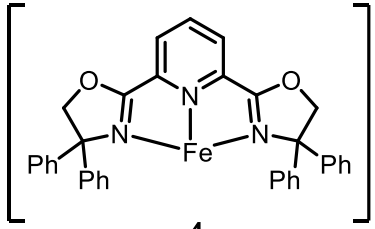
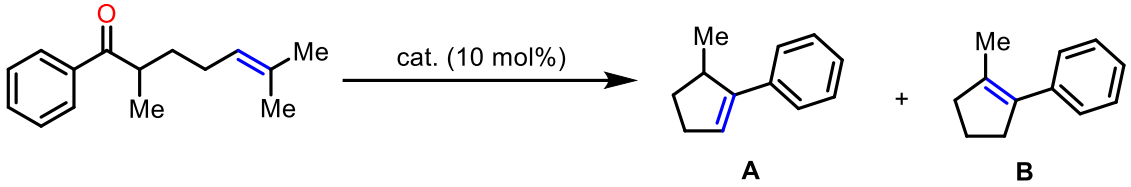


4

Further Development

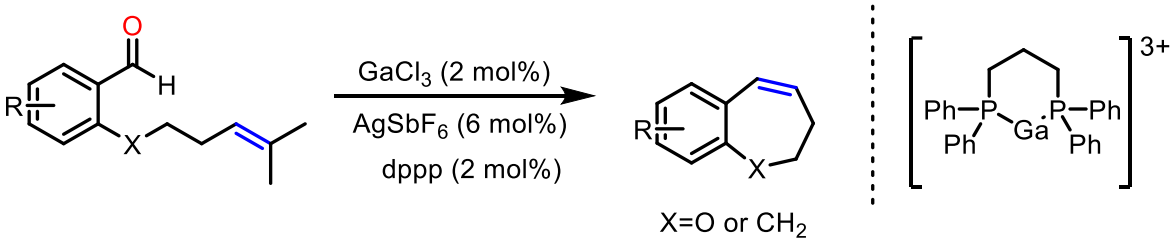
- *in situ* Isomerization

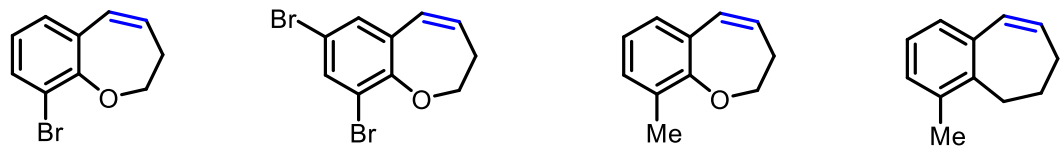


A **B**

LA	yield of **A**	yield of **B**
2	8%	0%
$FeCl_3$	40%	14%
3	45%	21%
$FeCl_3$ dimer	9%	67%
4	15%	84%
$[FeCl_2][SbF_6]$	0%	85%

- Seven Membered Ring



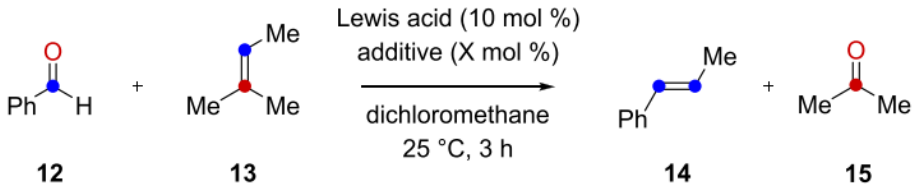


Outline

- Introduction
- Ring-Closing COM
- Other-Type COM
- Summary and Acknowledgement

Cross COM

■ Catalyst and Additive

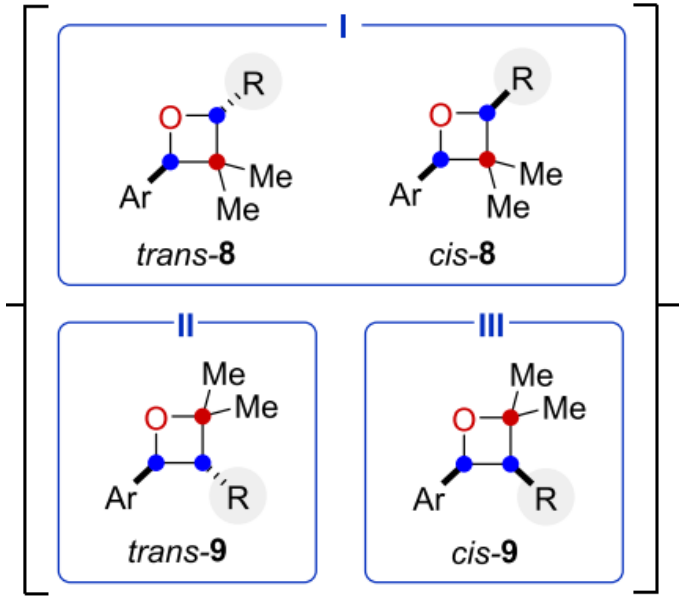


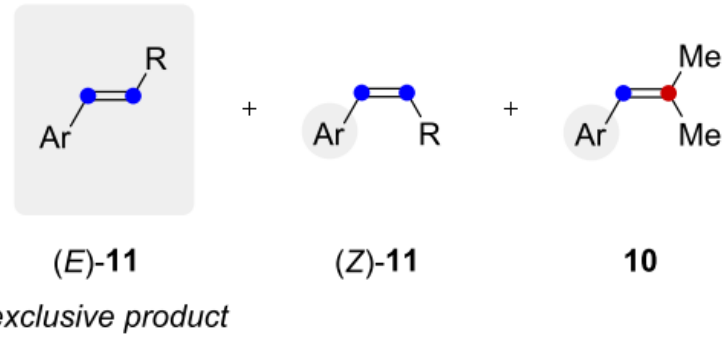
12 13 14 15

entry	species	Lewis acid	additive	X mol %	yield **14** (%)
1[b]	A	$FeCl_3$	–	–	19
2[c]	B	–	$AgBF_4$	30	0
3[d,e]	C	$FeCl_3$	$AgBF_4$	10	20
4[c,e]	**D**	**$FeCl_3$**	**$AgBF_4$**	**30**	**51**
5[c]	E	$FeCl_3$	AgF	10	4
6[c]	F	$FeCl_3$	AgF	30	9
7[b]	F	FeF_3	–	–	0
8[b]	G	$BF_3{\cdot}Et_2O$	–	–	28

- ✓ Exceeded **12** (5:1)
- ✓ *E*-Selectivity

■ Regio-Selectivity

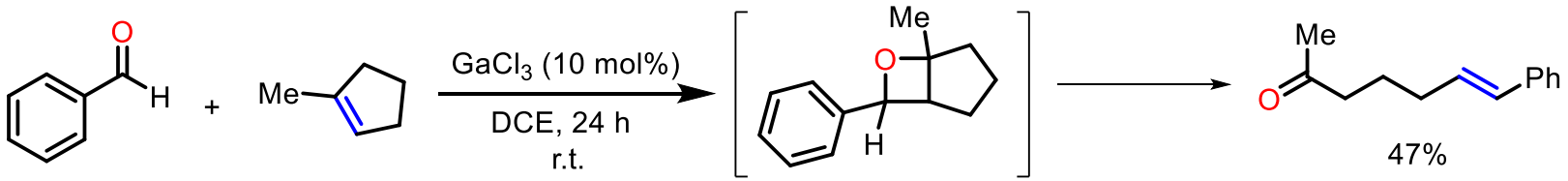




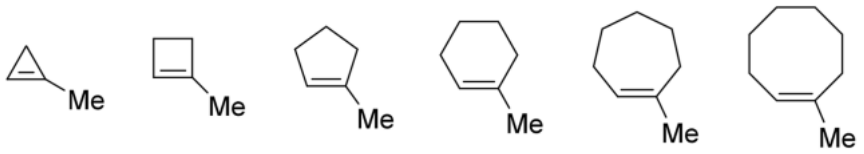
Schindler, C. S. *et al. Org. Lett.* **2020**, 22, 8, 3155–3160

Ring-Opening COM

- Reaction Condition

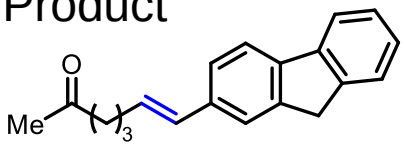


- Ring Strain

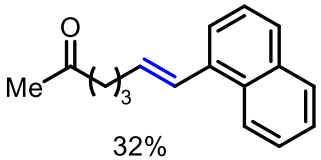


	14	15	12	16	17	18
RSE[a]	54.5	29.7	5.0	1.7	6.3	7.4
reactivity[b]	0%	-	47%	18%	0%	0%

- Selected Product



45%



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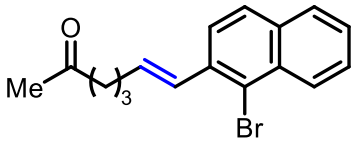

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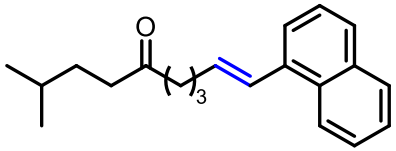

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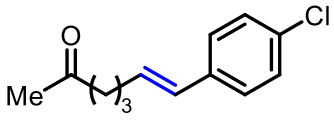

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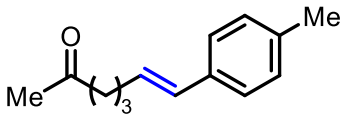
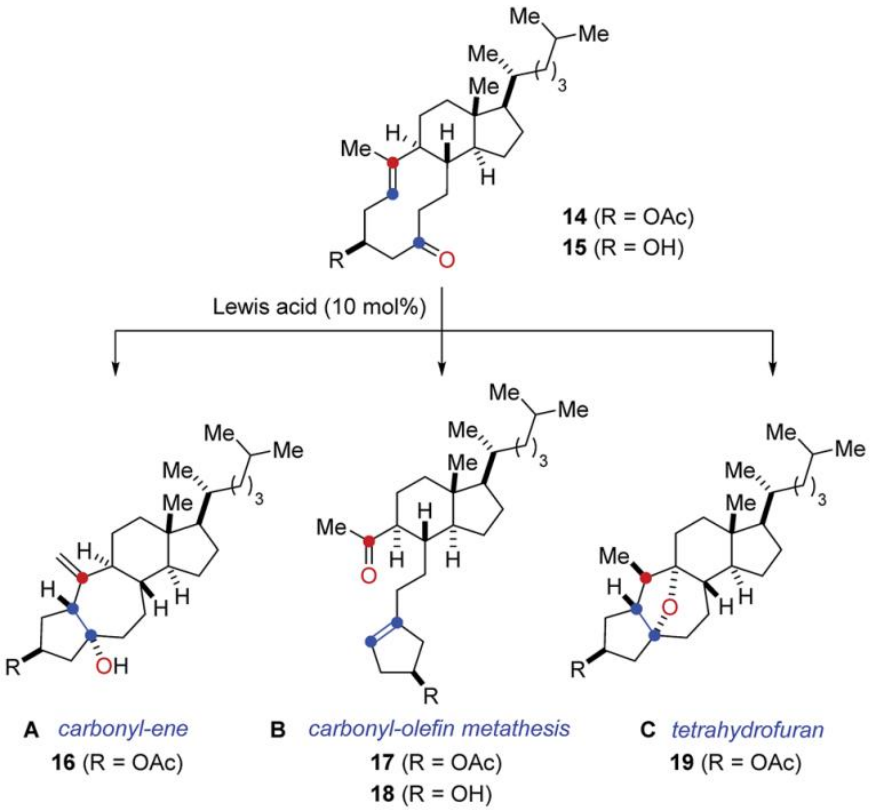


32%

Schindler, C. S. *et al. Org. Lett.* **2018**, 20, 16, 4954–4958

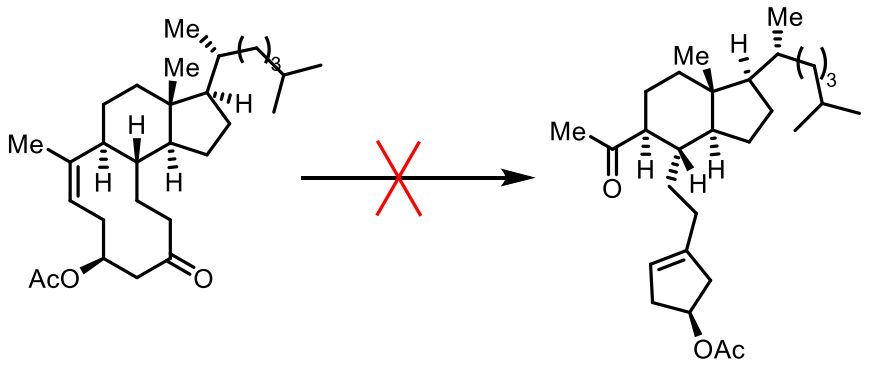
Transannular COM

■ Effect of Lewis Acid

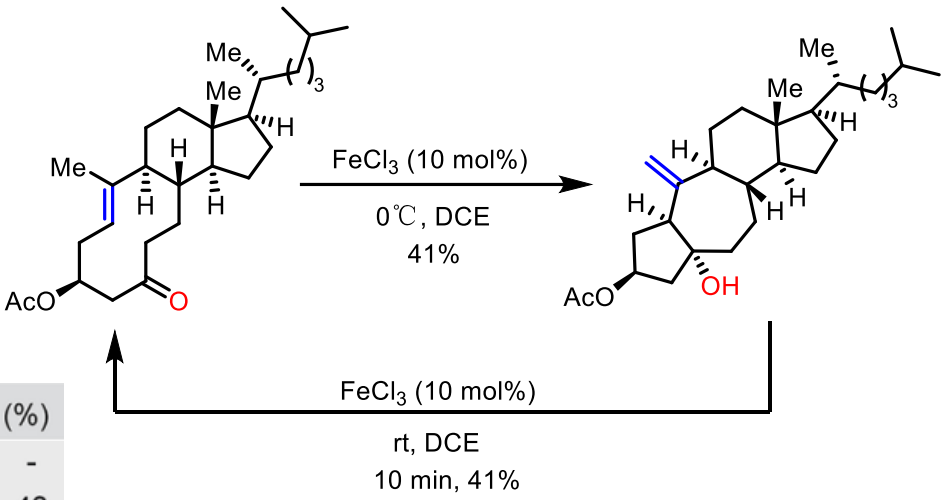


Lewis acid	mol%	R	yield **A** (%)	yield **B** (%)	yield **C** (%)
$FeCl_3$	10	OH	-	75	-
$TiCl_4$	10	OAc	-	-	43
Me_2AlCl^a	100	OAc	85	-	-

■ Configuration of Olefin

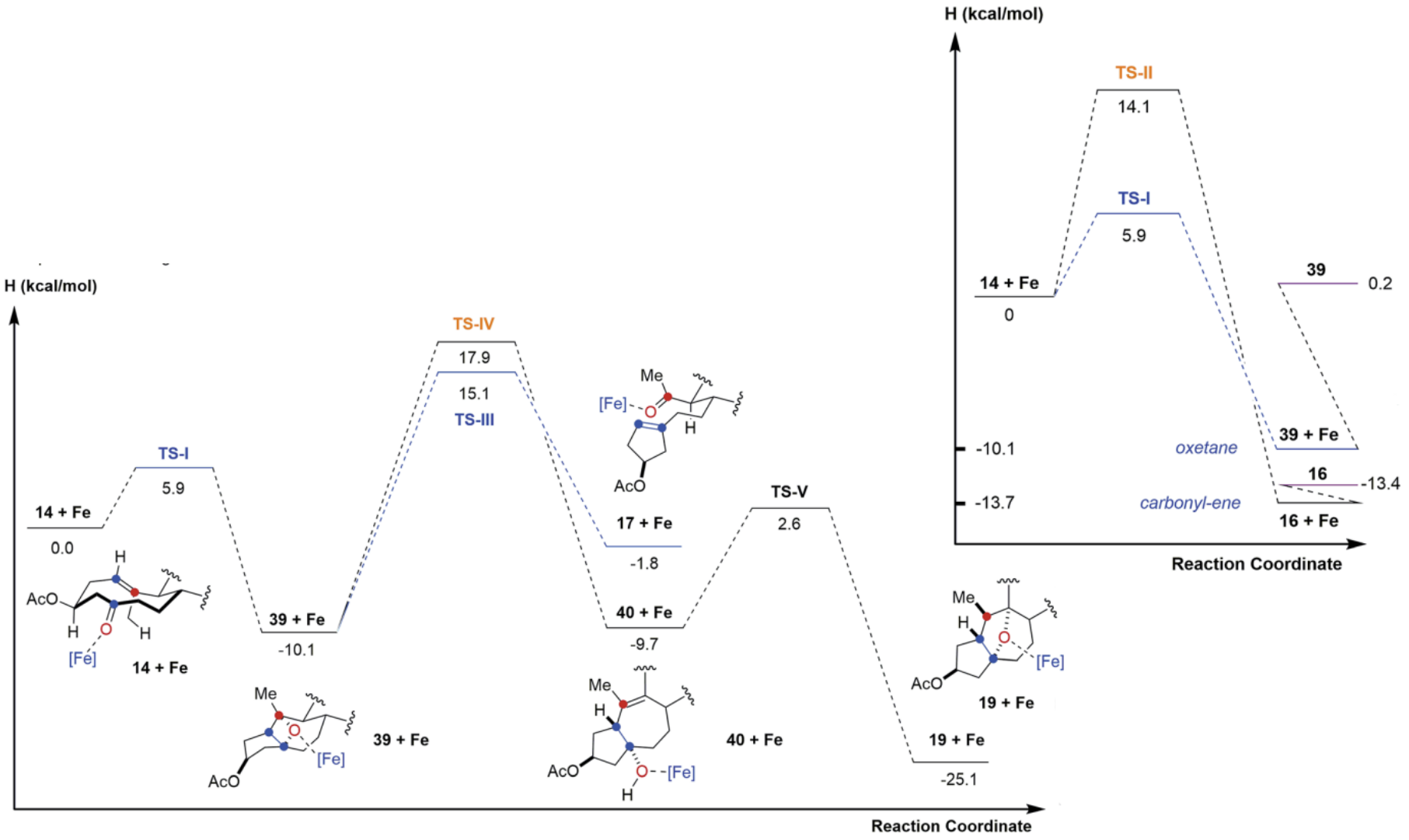


■ Equilibrium



Riehl, P. S.; Nasrallah, D. J.; Schindler, C. S. *Chem. Sci.*, **2019**, 10, 10267–10274

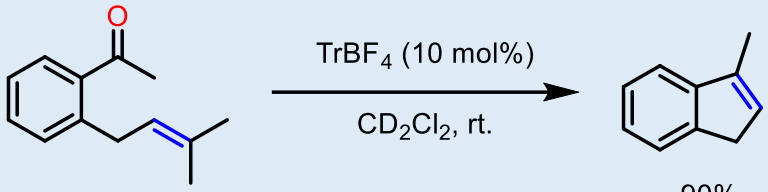
Mechanism



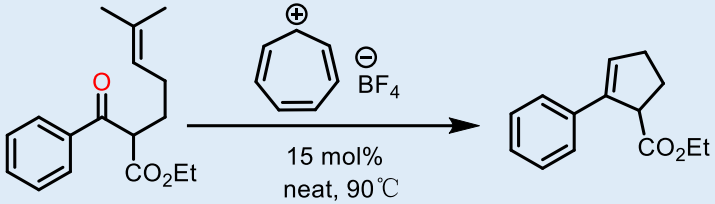
Riehl, P. S.; Nasrallah, D. J.; Schindler, C. S. *Chem. Sci.*, **2019**, 10, 10267–10274

Other Catalyst

■ Carbocation

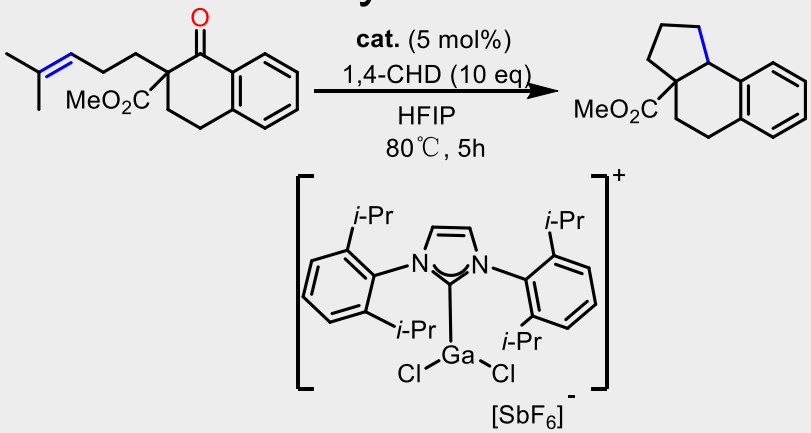


Ni, S.; Franzén, J. *Chem. Commun.,* **2018**, 54, 12982-12985



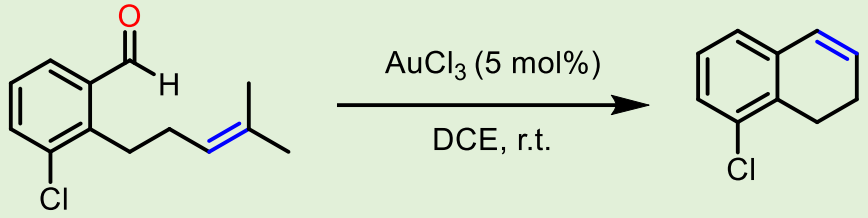
Nguyen, T. V. *et al. Chem. Sci.,* **2018**, 9, 5145–5151

■ Gallium-Catalyst



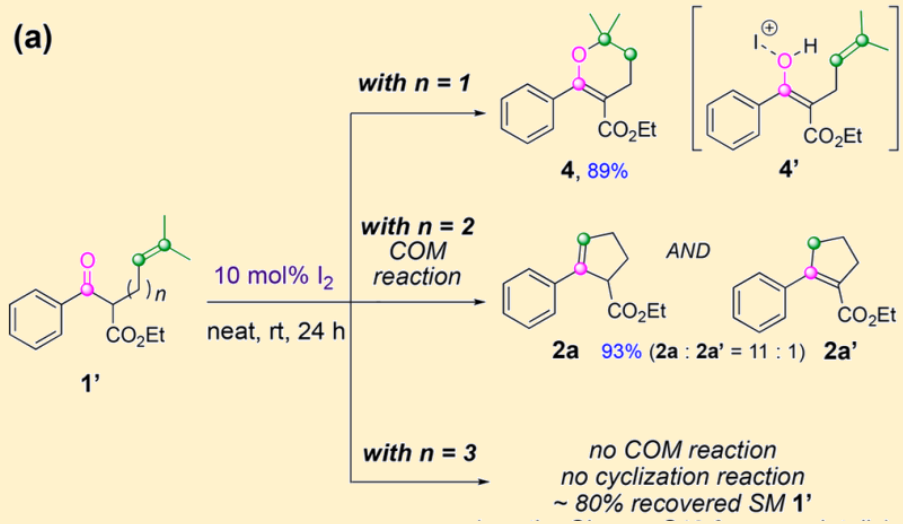
Gandon, V.; Bour, C. *et al. Org. Lett.* **2019**, 21, 19, 8132–8137

■ $AuCl_3$



Lin, Z. *et al. Chem.Eur.J.***2020**,26,1941 –1946

■ Molecular Iodine



Nguyen, T. V. *et al. ACS Catal.* **2019**, 9, 2, 912–919

Outline

- Introduction
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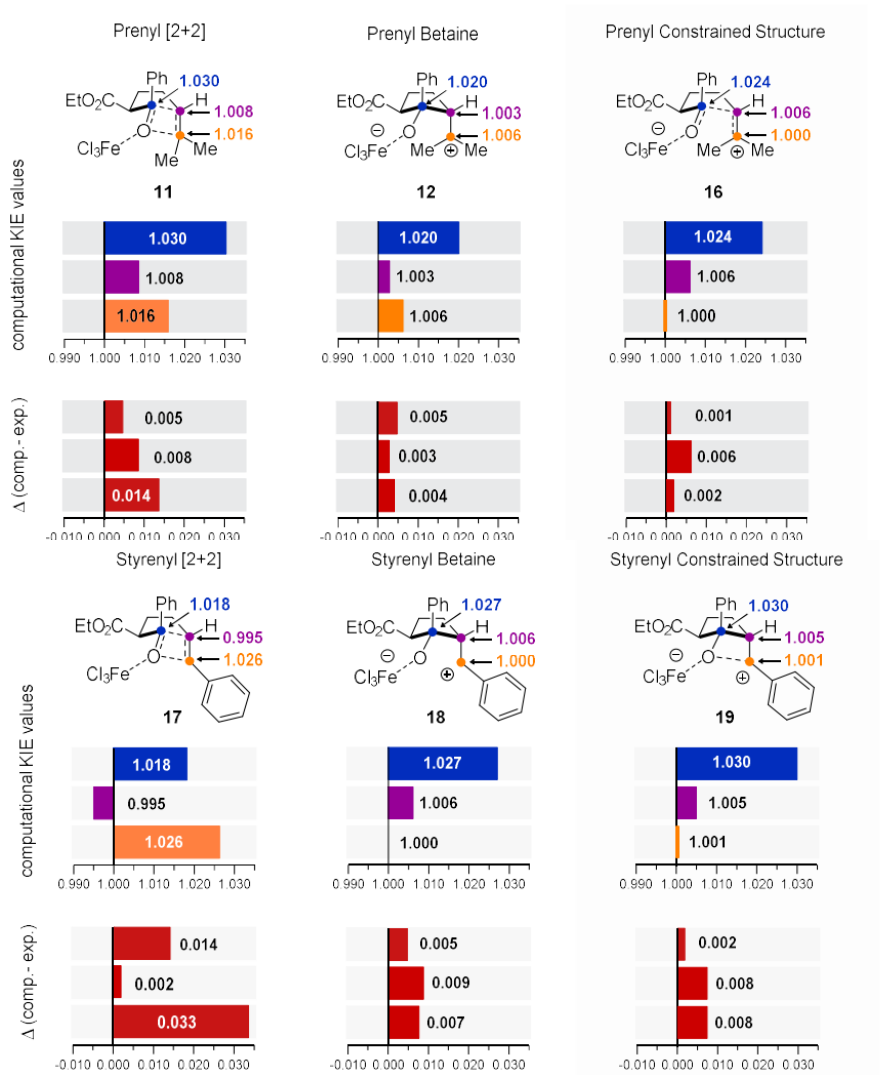
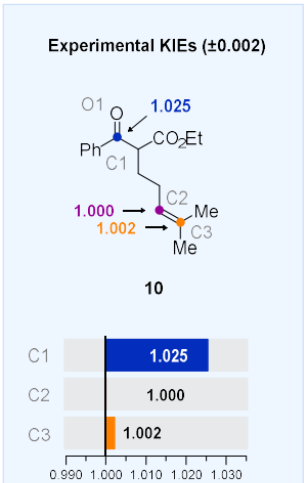
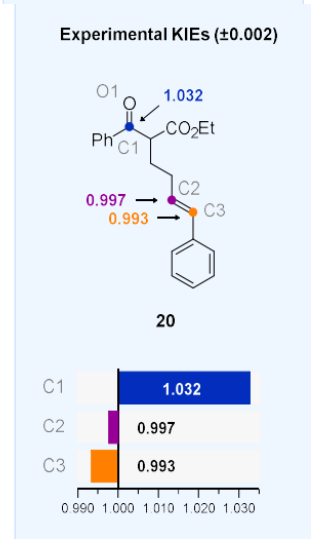
Latest Results

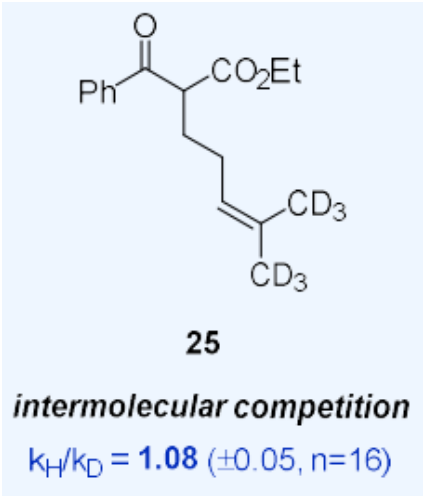
$^{12}C/^{13}C$ KIEs







H/D KIEs

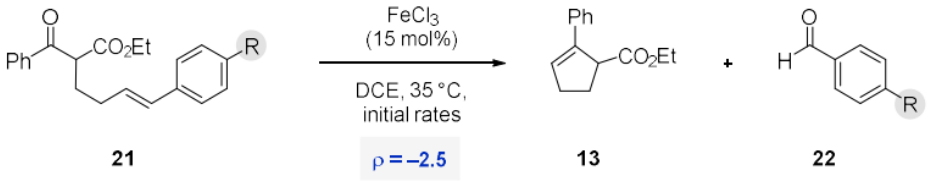


Intermolecular Competition Experiment

doi: 10.26434/chemrxiv-2022-nnp81

Latest Results

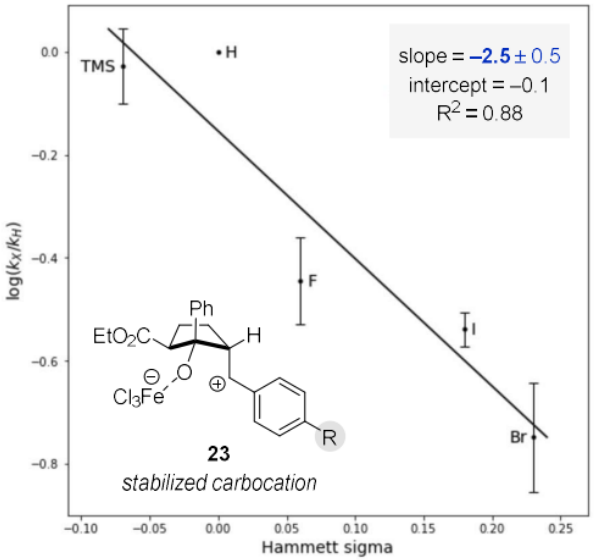
- Hammett Study



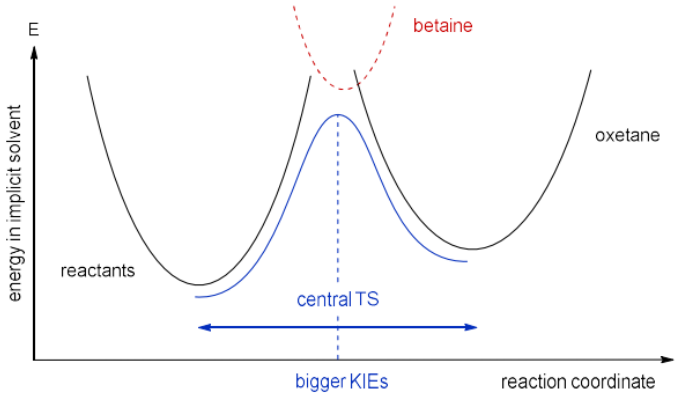
21 13 22

Substituents Evaluated

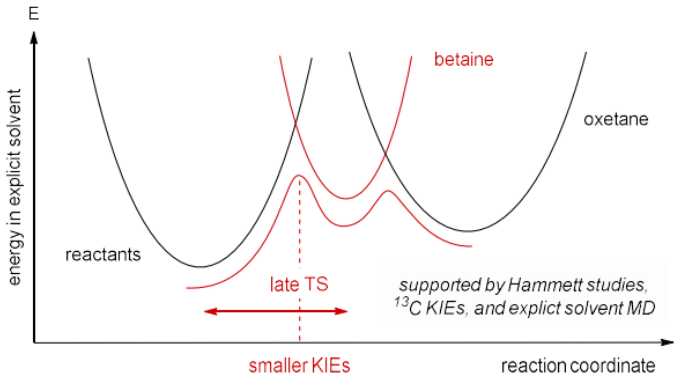
R	Me O	*t*Bu	Me	TMS	H	F	I	Br	CF_3
σ	-0.27	-0.20	-0.17	-0.07	0.00	0.06	0.18	0.23	0.53
	decomposition			*accessible substrates*					*unreactive*



- Marcus Theory



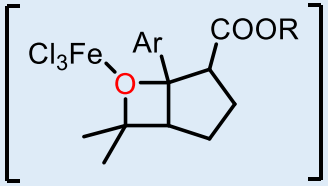
Implicit Solvent Model



Explicit Solvent Model

Summary

■ Mechanism



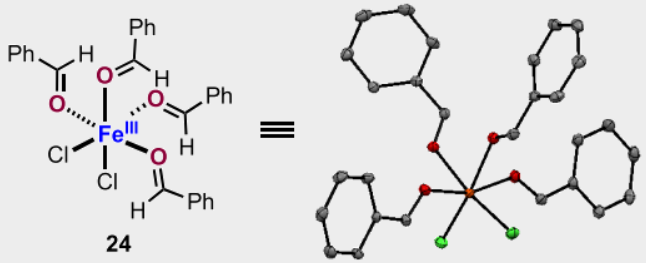
Intermediate

Concerted vs. Carbocation

■ Substrates Scope

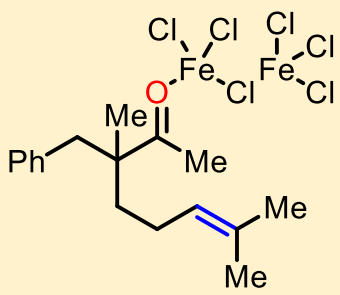
Aryl Ketone or Aldehyde
Mainly Five-Membered Rings

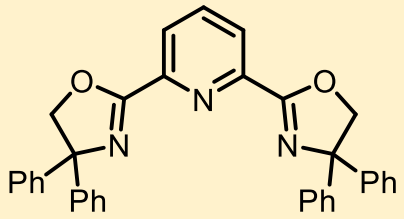
■ Byproduct Inhibition



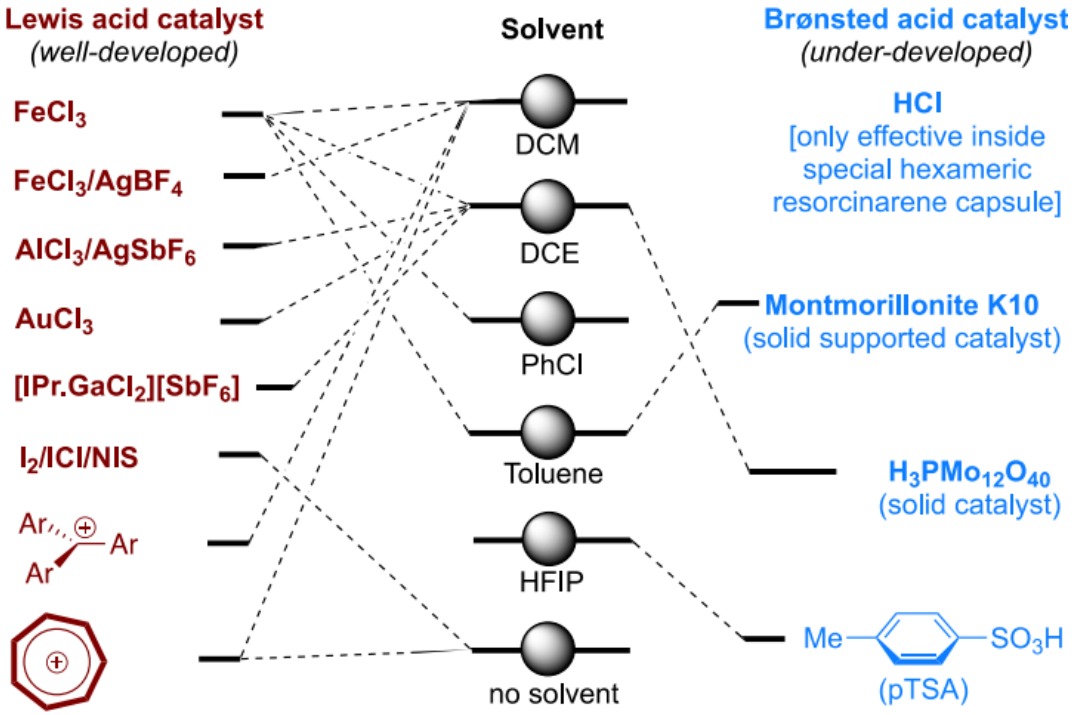
■ Tuning Lewis Acidity

$[AlCl_2][SbF_6]$

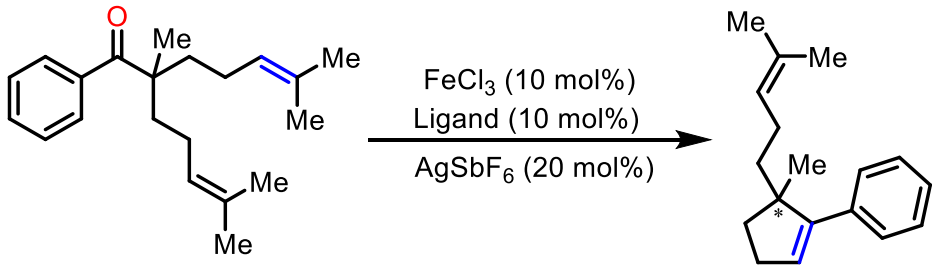




Perspective



- Broaden the Substrates Scope
- Other Type of COM
- Construction of Charity Center



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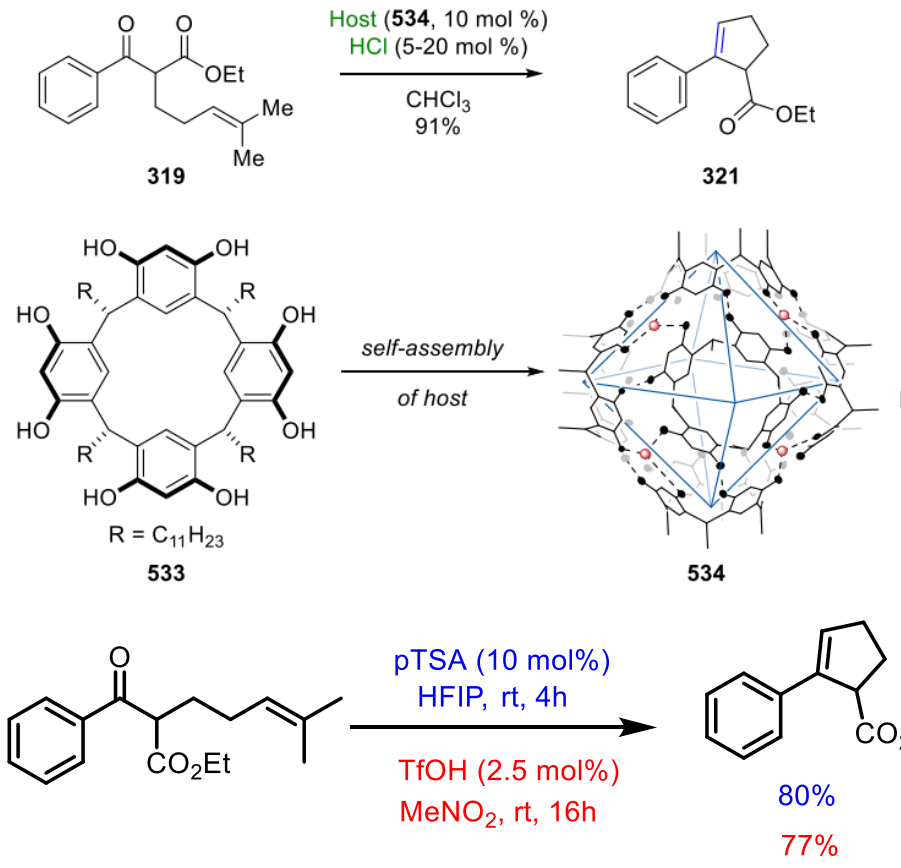
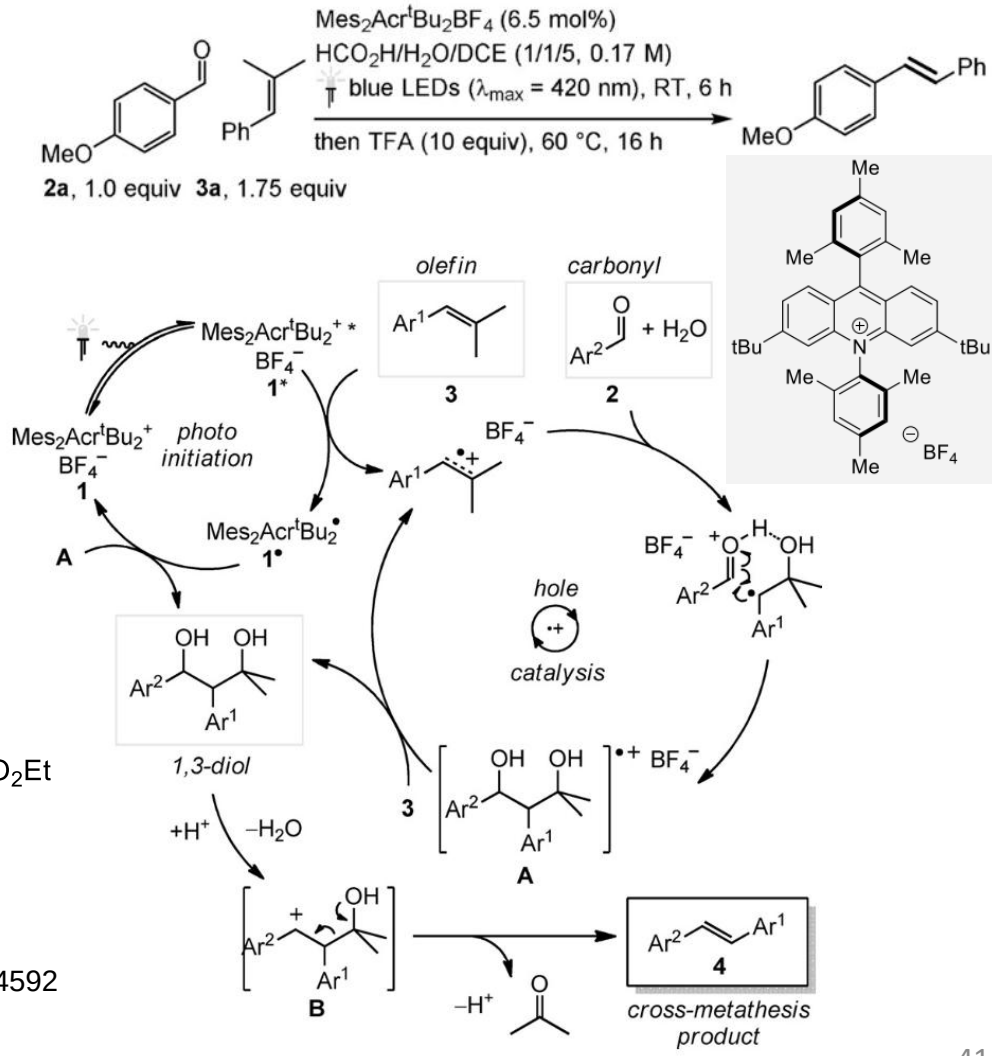
Perspective

■ Brønsted Acid



■ Visible-Light-Mediated Approach



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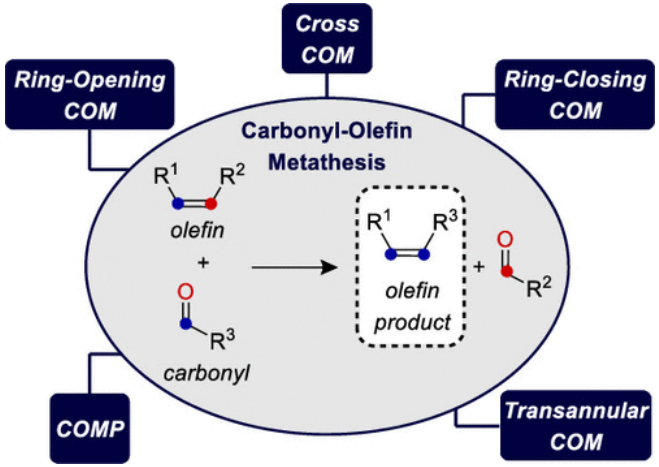
Overall Reference



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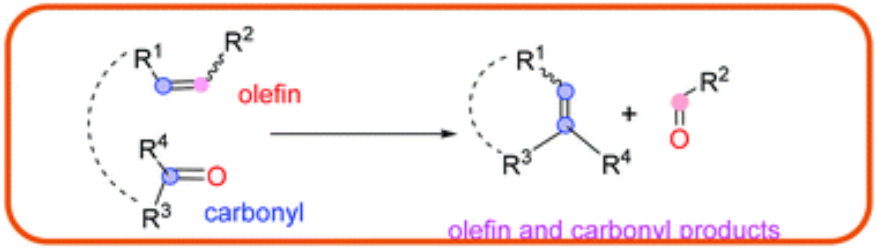

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- Unpublished results partly come from *Overcoming Limitations in Carbonyl-Olefin Metathesis Through Novel Catalytic Approaches* by Ashlee J. Davis, University of Michigan (https://dx.doi.org/10.7302/4785)