Olefin Metathesis Reaction: A Story of Catalyst Development

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Outline

- **Introduction**
- **Classical Catalysts System**
  Schrock Catalysts
  Grubbs Catalysts
  RCM Reaction
  Classical CM Reaction
- **Catalysts Improvement**
  Restrictions of Classical Catalysts
  Solutions of Grubbs Catalysts
  Solutions of Schrock Catalysts
- **Summary**
- **Acknowledgement**

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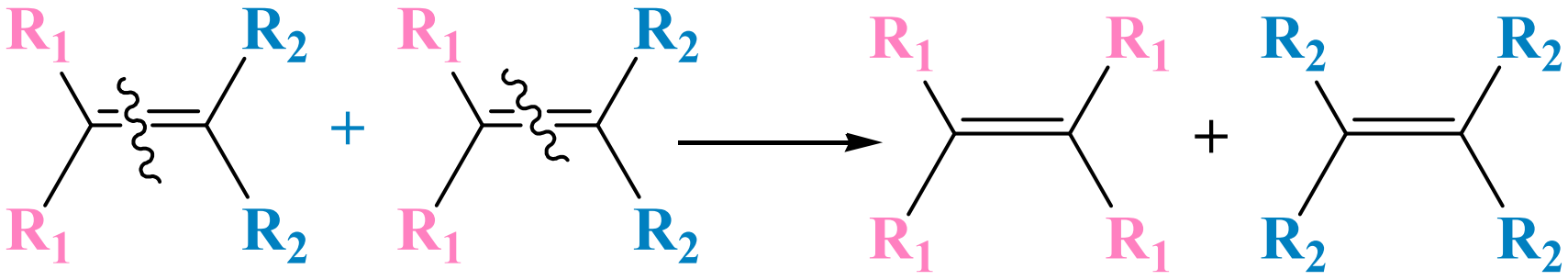
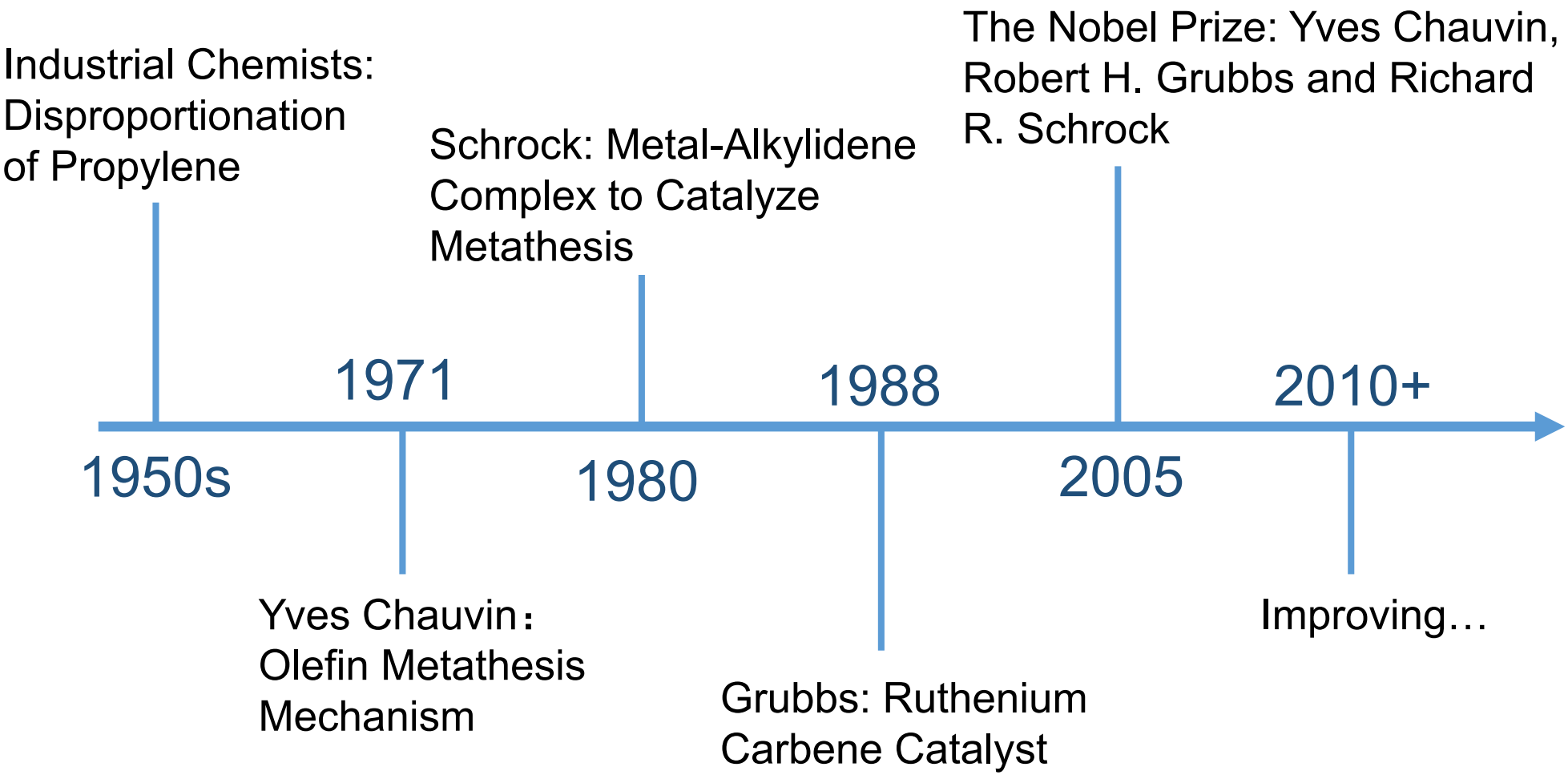
Introduction & History



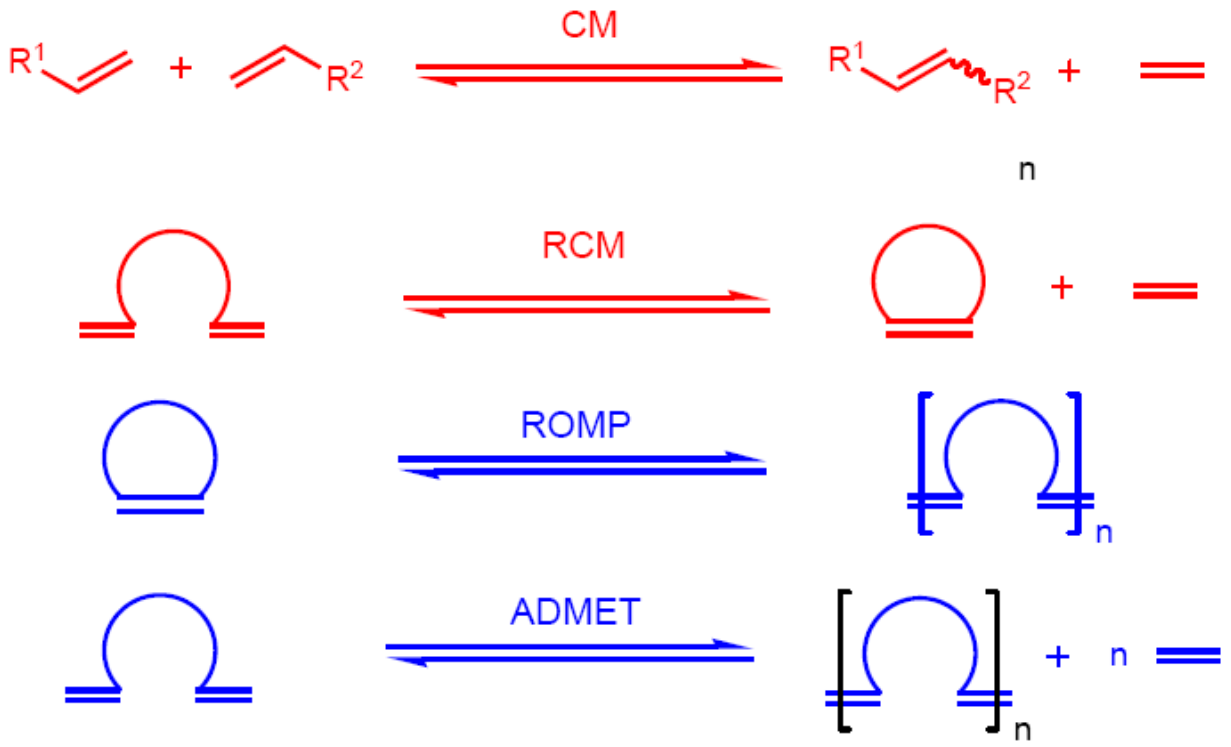
- At first two men were a pair, two women were a pair, and to shouts of “ catalyst! " they crossed over and became two couples.

Introduction & History



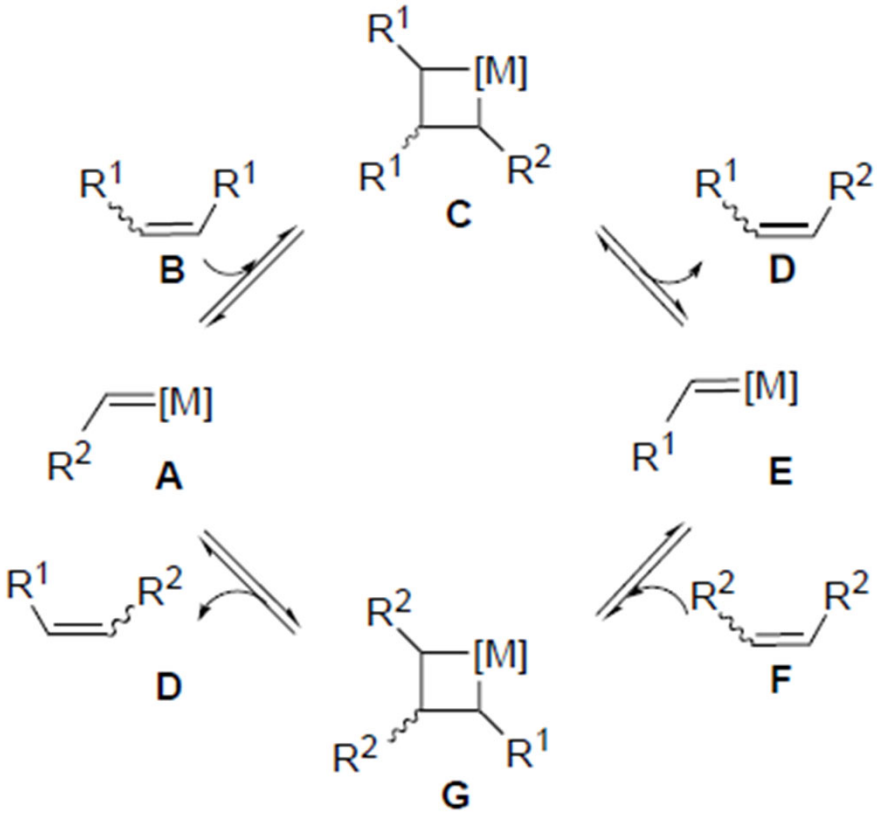
Basic Reaction Types

- **Cross Metathesis**
- **Ring Closing Metathesis**
- Ring Opening Metathesis Polymerization
- Acyclic Diene METathesis

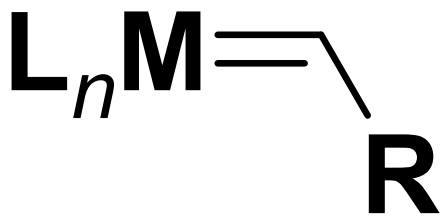


Classical Mechanism

- Most Important Intermediate: **Metal-Carbene**



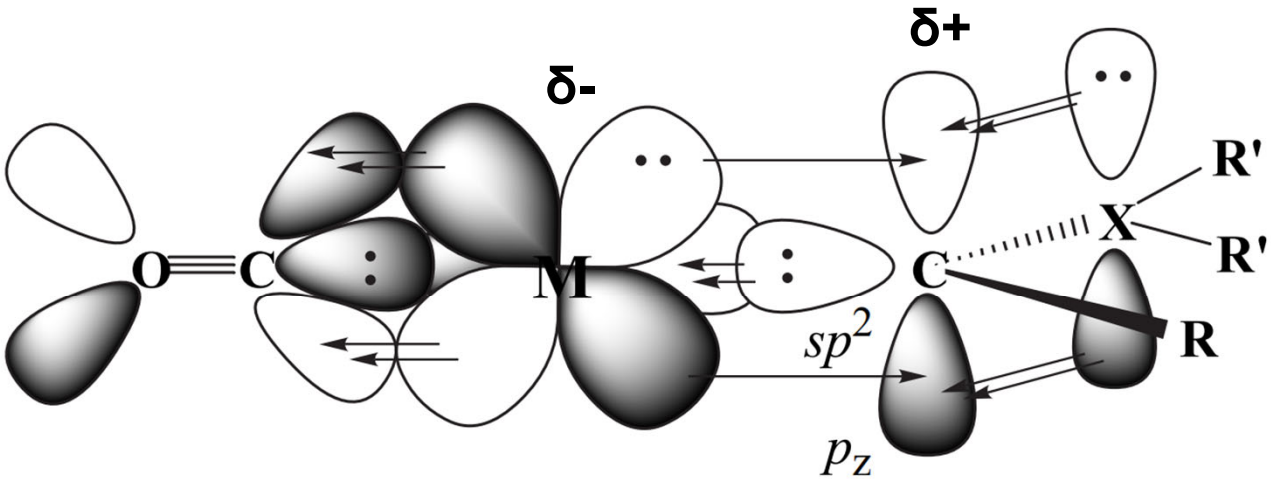
For Olefin Metathesis:
Suitable?

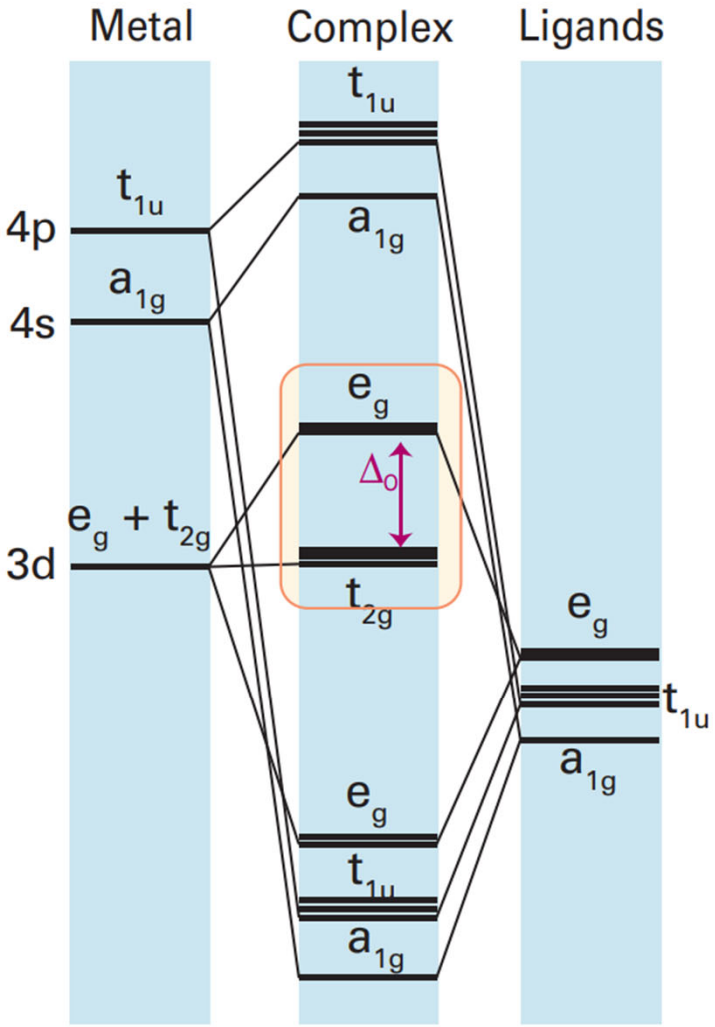


Chauvin, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3740.

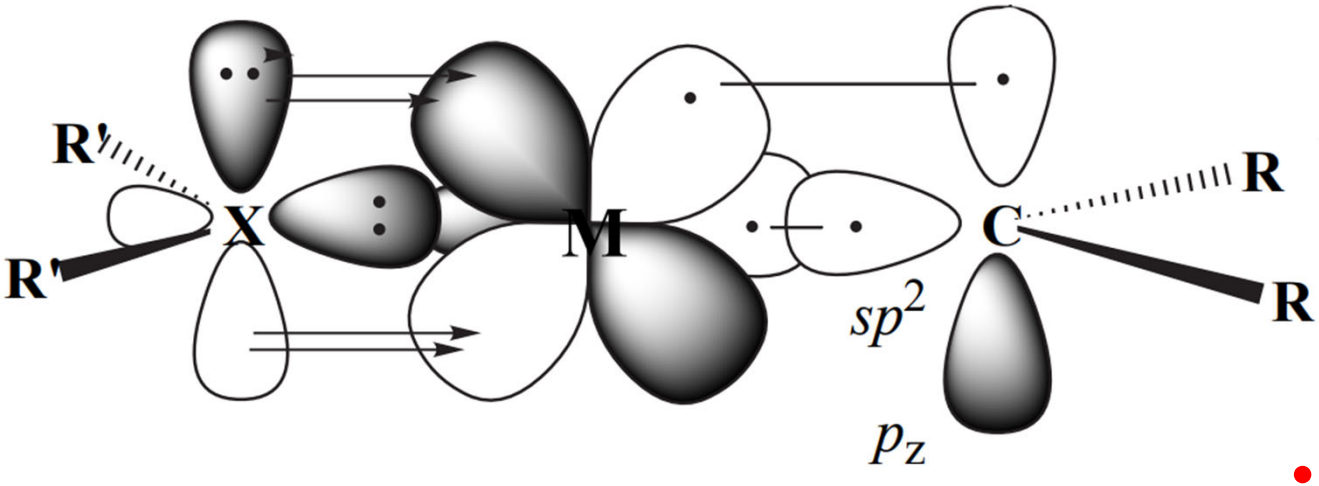
Types of Metal-Carbene: Fischer

- **Low** Oxidation State
- **Late** Metals
- Electrophilic Carbon
- Singlet-Like Carbene

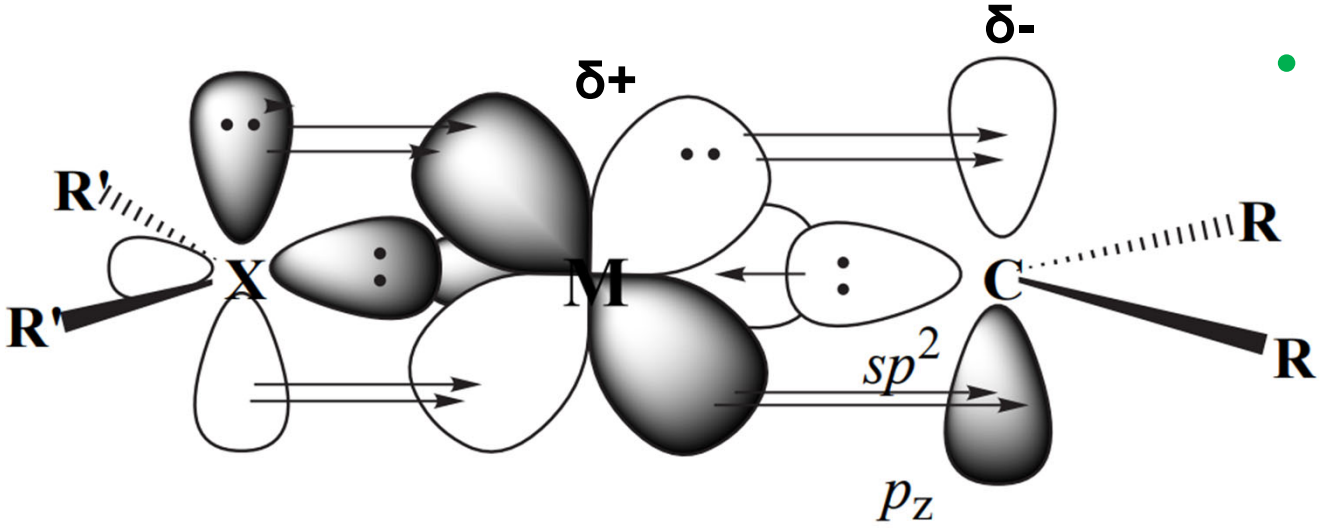




Types of Metal-Carbene: Schrock



- **Normal**-Schrock:
- Less Polarization
- Triplet-Like Carbene
- **Metathesis Suitable**

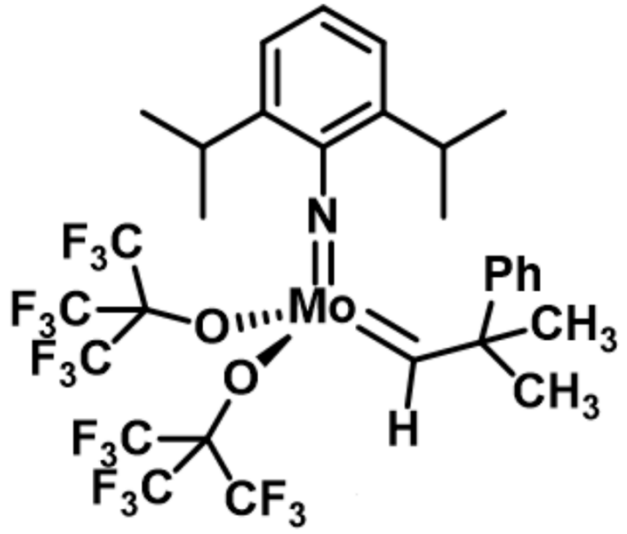


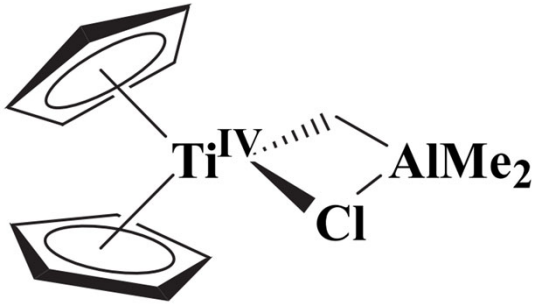
- **High** Oxidation State
- **Early** Metals

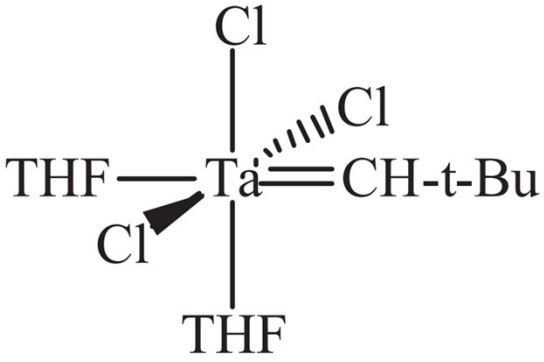
- **Extreme**-Schrock:
- Nucleophilic Carbon
- Contrary to Fischer

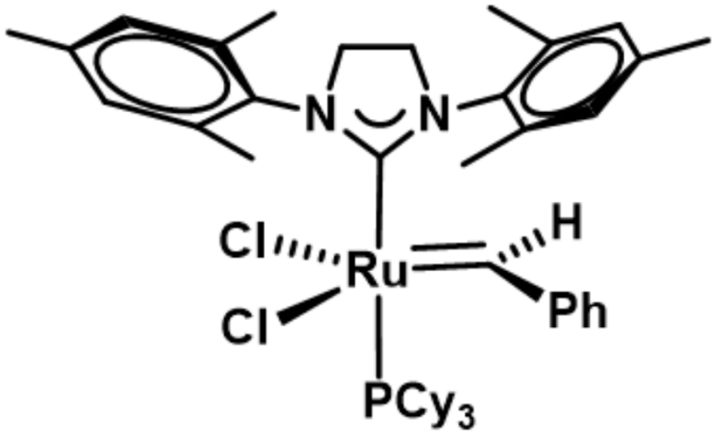
Classical Metal Center: Mo & Ru

- Second Transition Series
- **Moderate** Electronegativity
- Variable Coordination Number
- Different Between **Mo** & **Ru**?
- Accidental Discovery & Rational Design









Grubbs, R. *J. Am. Chem. Soc.* **1982**, *104*, 7491.; Schrock, R. *J. Am. Chem. Soc.* **1974**, *96*, 6796.

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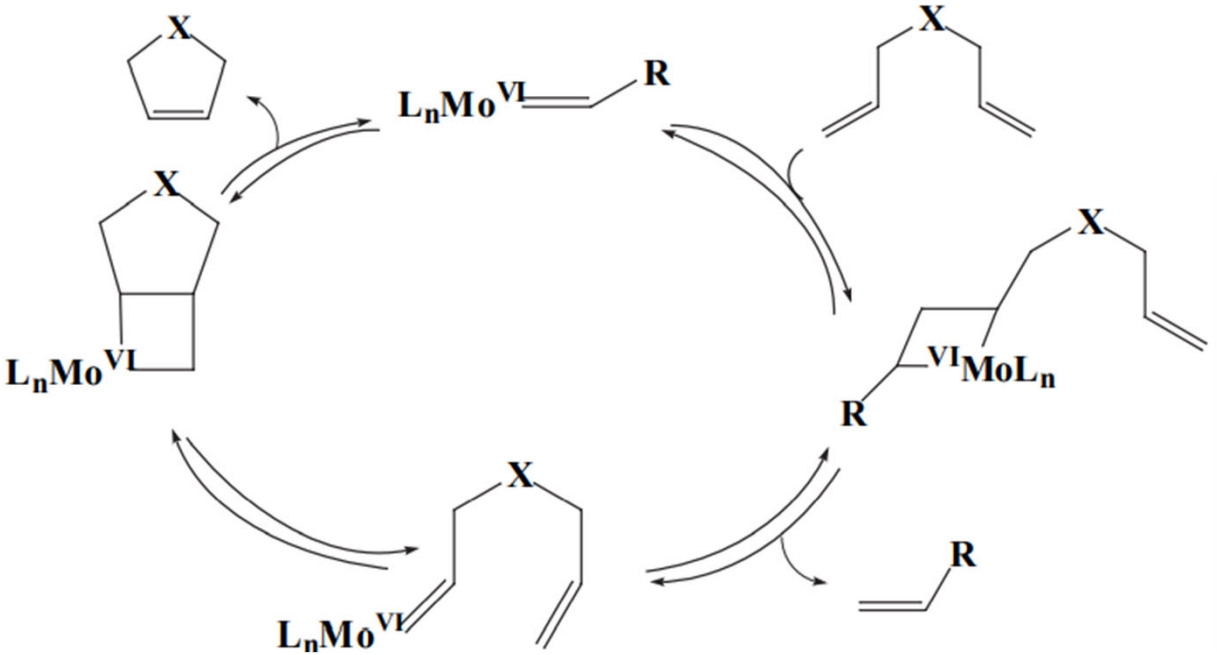
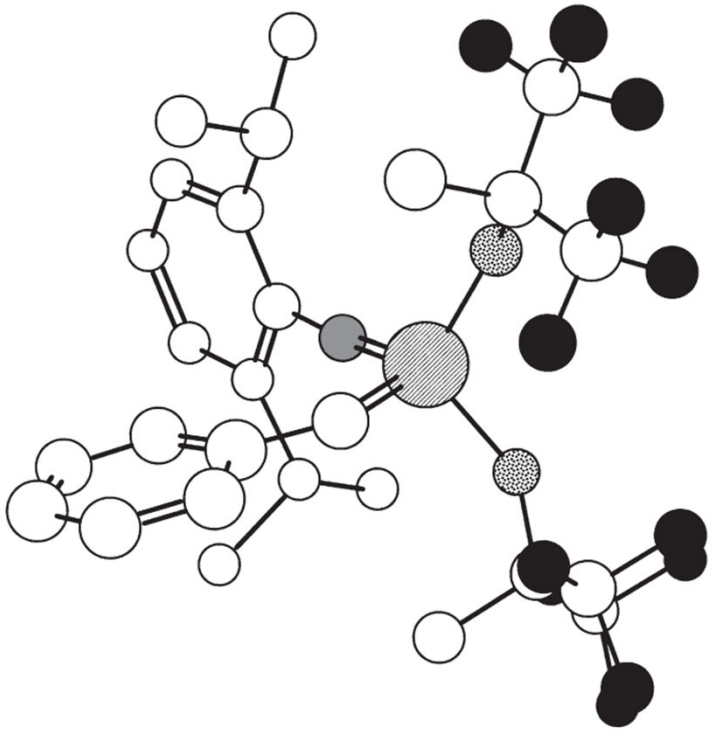
Schrock: Structure & Mechanism

- d^0: **Hard** and **Hard** to Form Normal Alkene-Complex
- Direct Four-Membered Ring Formation
- Steric **Sensitive** and **Tolerance**

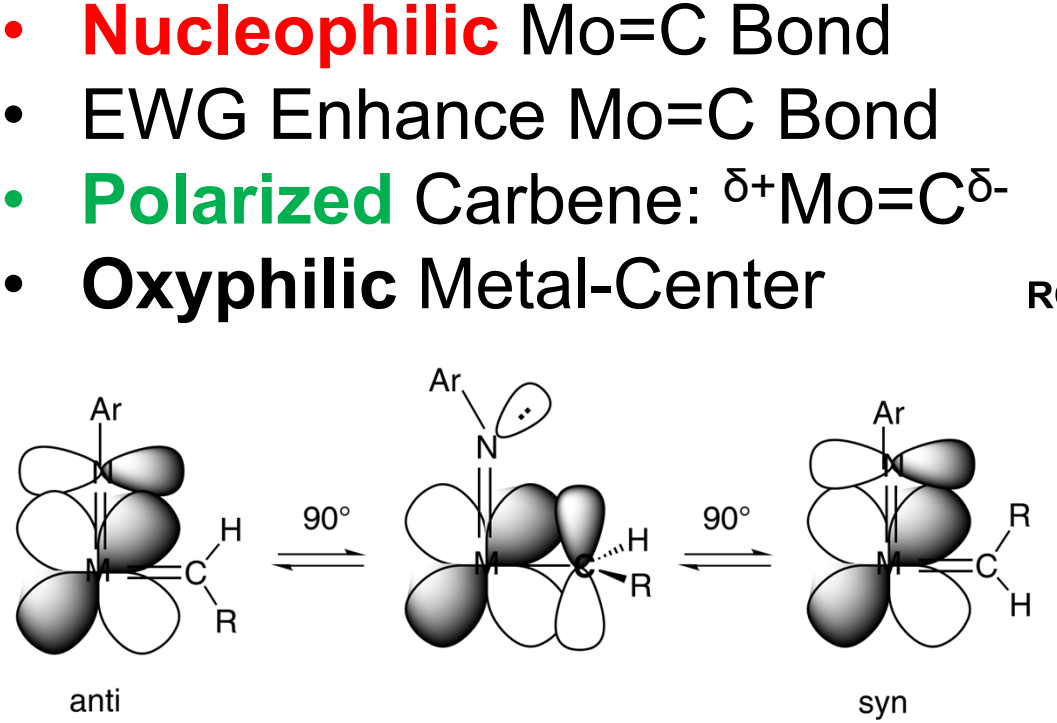


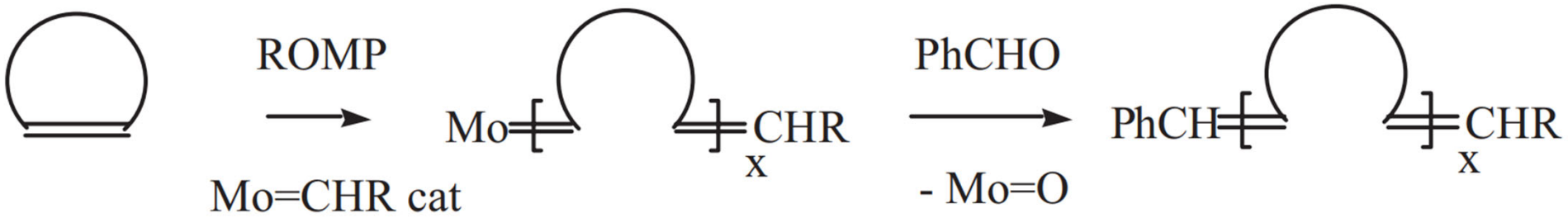


Schrock, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 3748.

Schrock: Nucleophilic Carbene

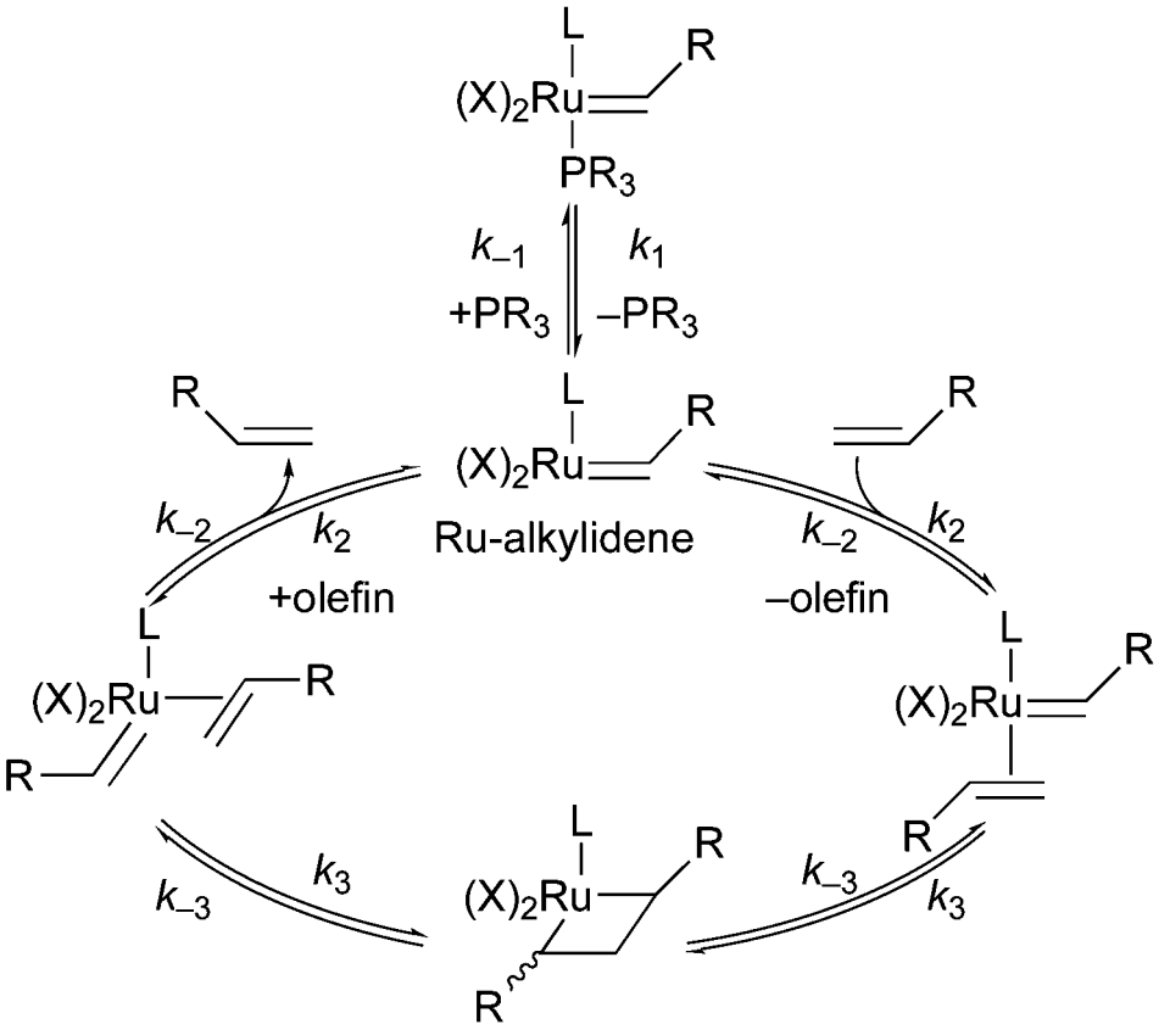
- **Nucleophilic** Mo=C Bond
- EWG Enhance Mo=C Bond
- **Polarized** Carbene: $^{\delta+}Mo=C^{\delta-}$
- **Oxyphilic** Metal-Center

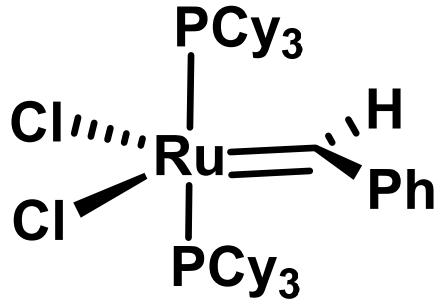




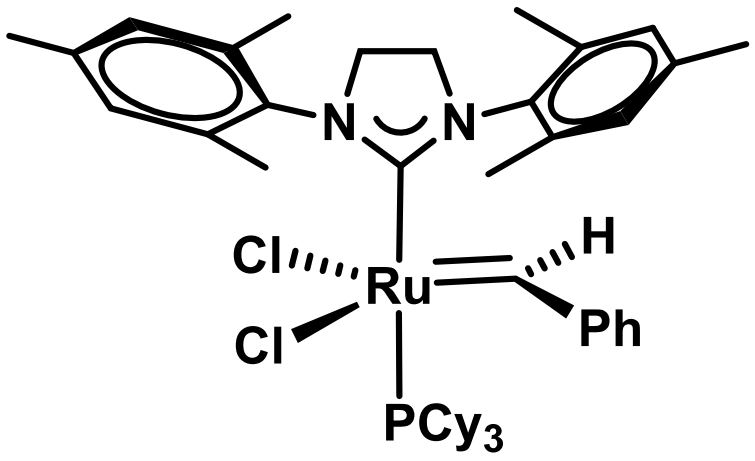
Schrock, R. et al. *J. Am. Chem. Soc.* **1993**, *115*, 11831.

Grubbs: Tetragonal Pyramid Catalysts



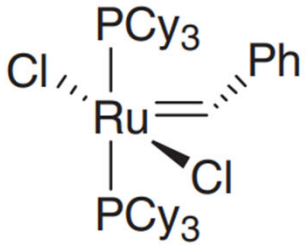
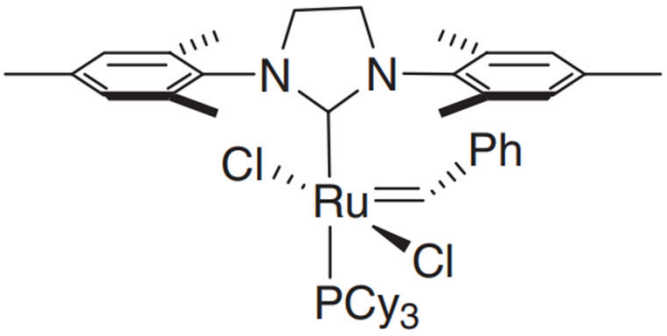


Grubbs I



Grubbs II

Efficiency Determination: k_1 & k_{-1}/k_2

	Initiation k_1 (per PCy_3)	Propagation k_{-1}/k_2
 **1**	$9.6 \pm 0.2\ s^{-1}$	13,000
 **2**	$0.13 \pm 0.01\ s^{-1}$	1.25

better initiation ↑

better propagation ↓

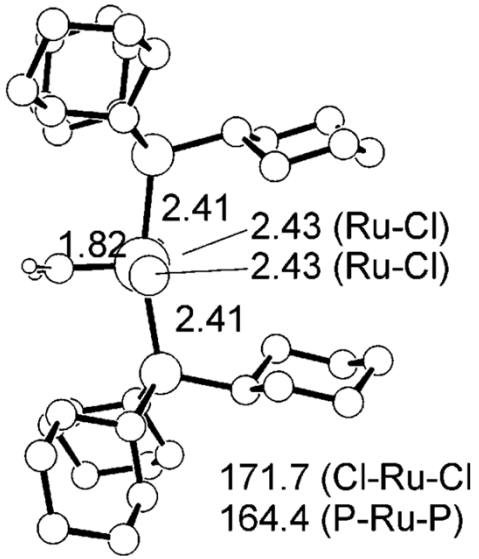
Grubbs, R. et al. *J. Am. Chem. Soc.* **2001**, *123*, 749.

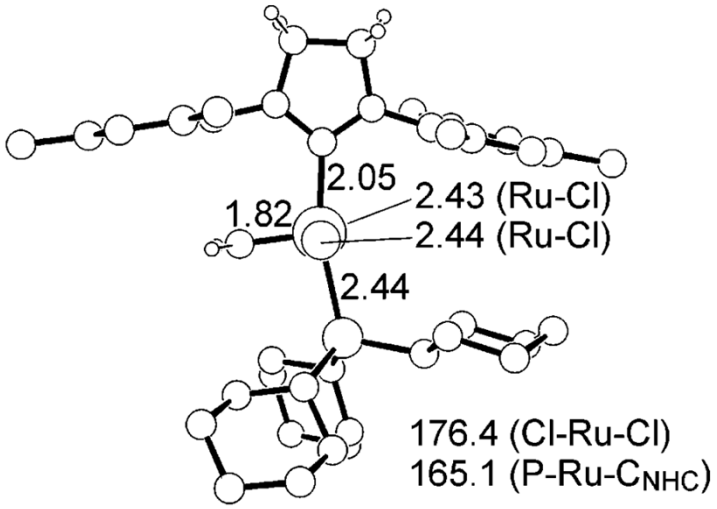
Roles that NHCs Play

k_1

NHC vs. Phosphine

- **Strong Donor**
- **Weak Accepter**
- *Trans*-Effect?

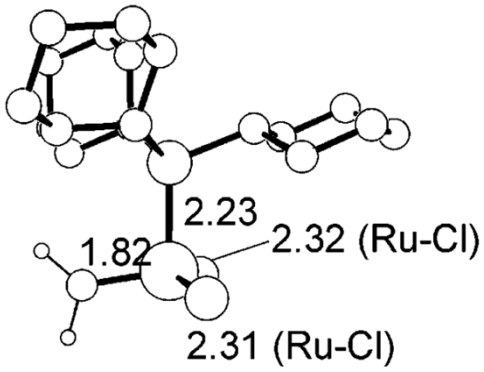


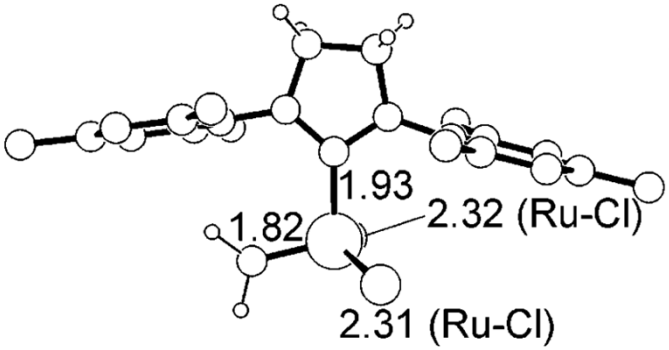


k_{-1}/k_2

Alkene vs. Phosphine

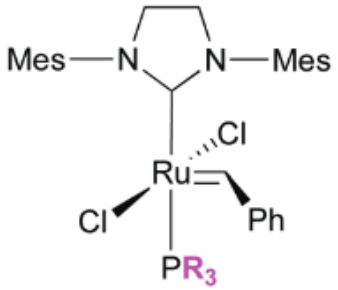
- **Weak Donor**
- **Strong Accepter**
- Circulation Efficiency





Chen, P. et al. *J. Am. Chem. Soc.* **2004**, *126*, 3496.

Influenced by Phosphine Ligands

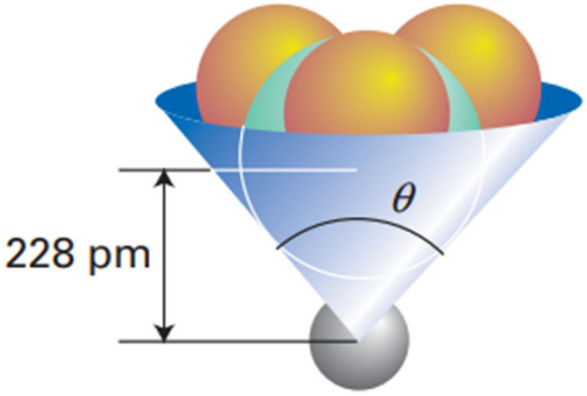


Ru-2-I–PR$_3$

Phosphine: Increase k_1/k_{-1}

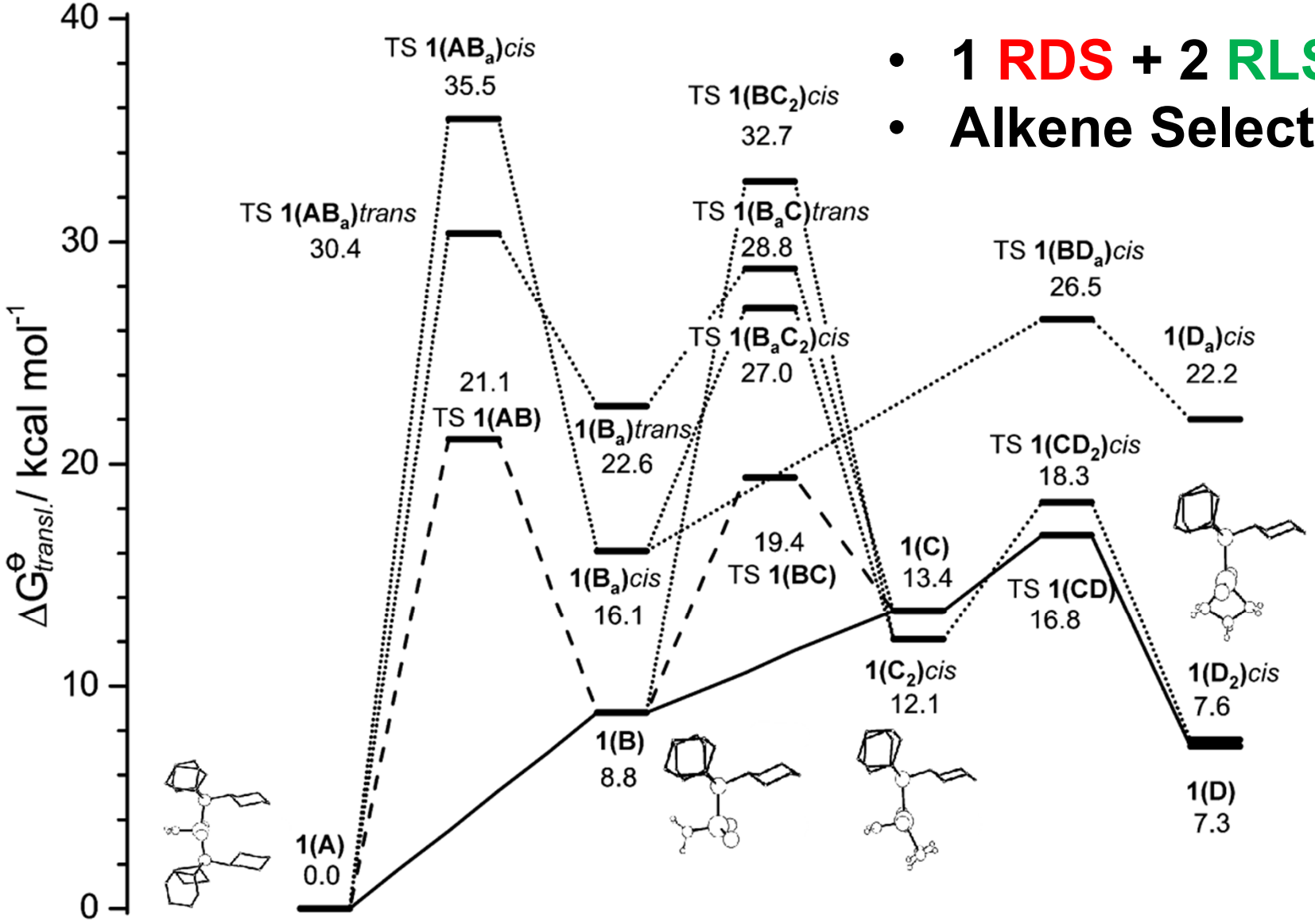
- **Electronic Deficient**
- **Large Cone Angle**

Entry	Catalyst–PR$_3$	(s^{-1})	k_{rel}[a]
I	**Ru-2-I**–PCy_3	0.13 ± 0.01	1.0
II	**Ru-2-I**–P$(n\text{-Bu})_3$	8.1×10^{-4}	0.006
III	**Ru-2-I**–P$(Ph)_2(OMe)$	1.7 ± 0.4	13
IV	**Ru-2-I**–PPh_3	7.5 ± 0.6	58
V	**Ru-2-I**–P$(p\text{-}CF_3C_6H_4)_3$	48 ± 2	369
VI	**Ru-2-I**–P$(p\text{-}ClC_6H_4)_3$	17.9 ± 0.4	138
VII	**Ru-2-I**–P$(p\text{-}FC_6H_4)_3$	8.5 ± 0.2	65
VIII	**Ru-2-I**–P$(p\text{-}C_6H_5)_3$	7.5 ± 0.6	58
IX	**Ru-2-I**–P$(p\text{-}CH_3C_6H_4)_3$	4.1 ± 0.2	32
X	**Ru-2-I**–P$(p\text{-}CH_3OC_6H_4)_3$	1.8 ± 0.1	14



Grubbs, R. et al. *J. Am. Chem. Soc.* **2003**, *125*, 10103.

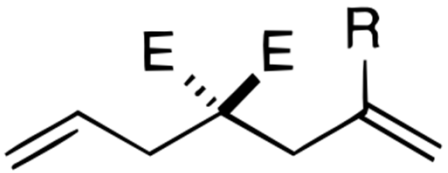
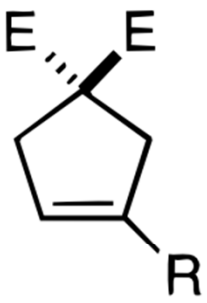
Mechanism Detail: Intermediate & RDS



- 1 RDS + 2 RLS
- Alkene Selectivity?

Chen, P. et al. *J. Am. Chem. Soc.* **2004**, *126*, 3496.

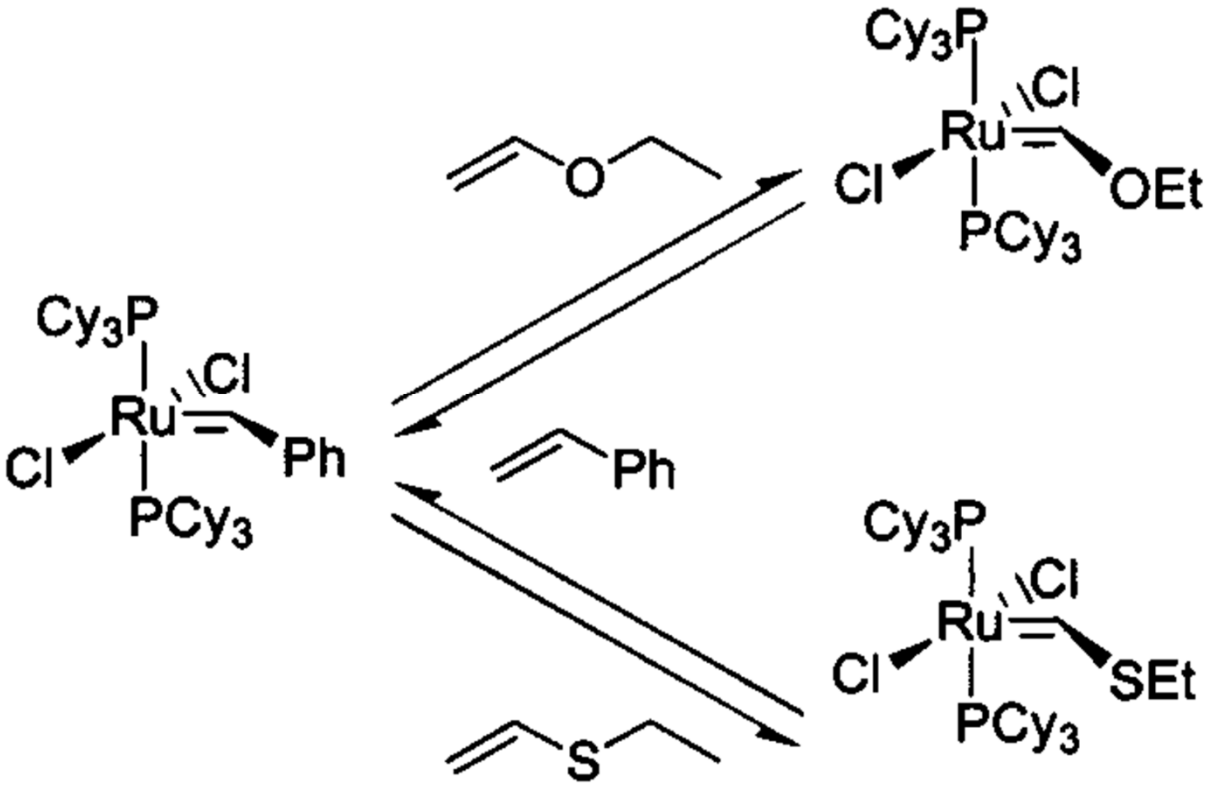
Electron-Rich & Less Steric Hindrance

Substrate		Product		Yield With **1**	Yield With **2**
					
R = Et	(**11a**)	R = Et	(**11b**)	93%	(100%)
R = ^{i}Pr	(**12a**)	R = ^{i}Pr	(**12b**)	98%	(100%)
R = ^{t}Bu	(**13a**)	R = ^{t}Bu	(**13b**)	NR	96%
R = Ph	(**16a**)	R = Ph	(**16a**)	(25%)	97%
R = CO_2Me	(**17a**)	R = CO_2Me	(**17b**)	(5%)	89%

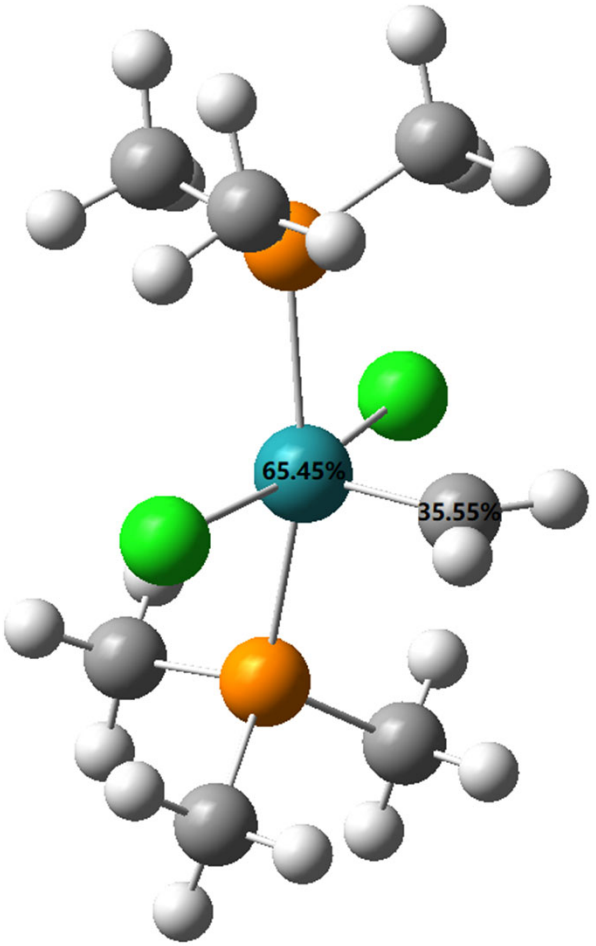
Grubbs, R. et al. *J. Org. Chem.* **1997**, *62*, 7310.

Regioselectivity & Fischer Tendency

- Regioselectivity for Alkenes
- Steric: **Ru-Part** Favored
- **EDG** vs. **EWG**: **Inertness** vs. **Activity**
- **Polarized** Carbene: $^{\delta-}Ru=C^{\delta+}$



NBO Distribution of Ru=C π Bond



PBE0(D3BJ)/def2tzvpp

Grubbs, R. et al. *Organometallics* **2002**, *21*, 2153.

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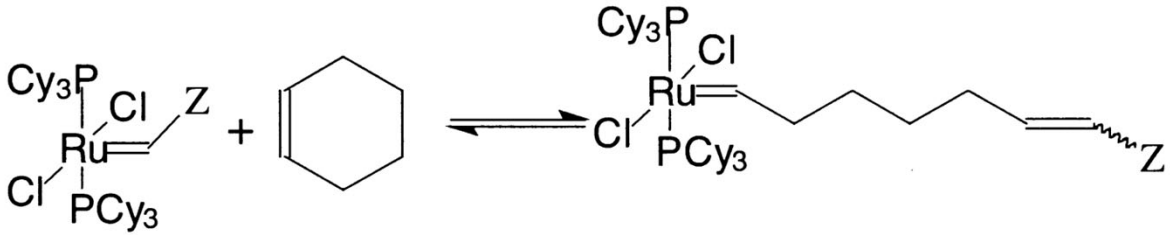

Z = CO_2-methyl
Z = CO_2-*p*-tolyl
Z = CO_2-*t*-butyl
Z = CO_2-*i*-propyl
Z = CO_2-cyclohexyl
Z = CO_2-1-adamantyl

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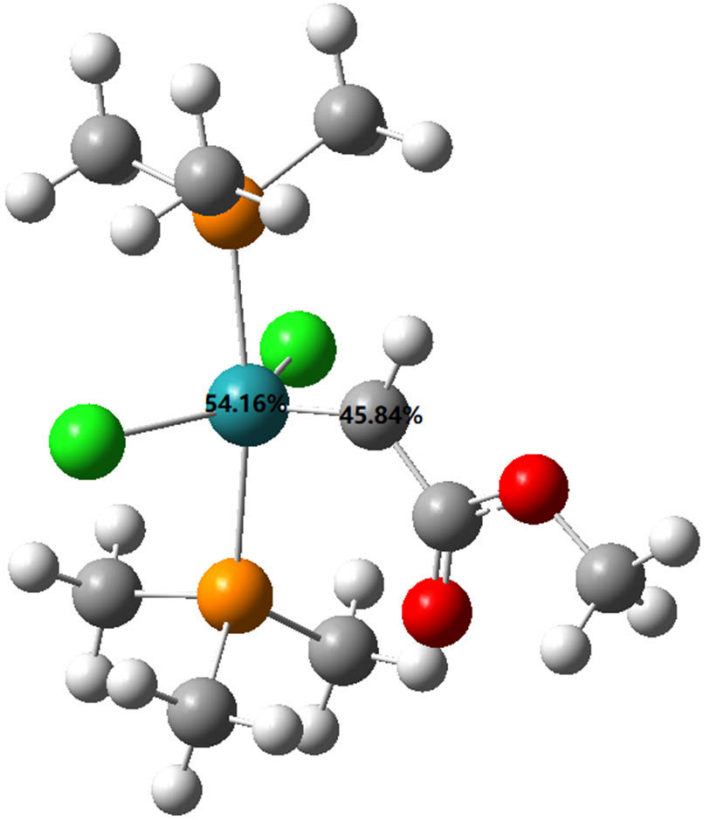
NBO Distribution of Ru=C π Bond



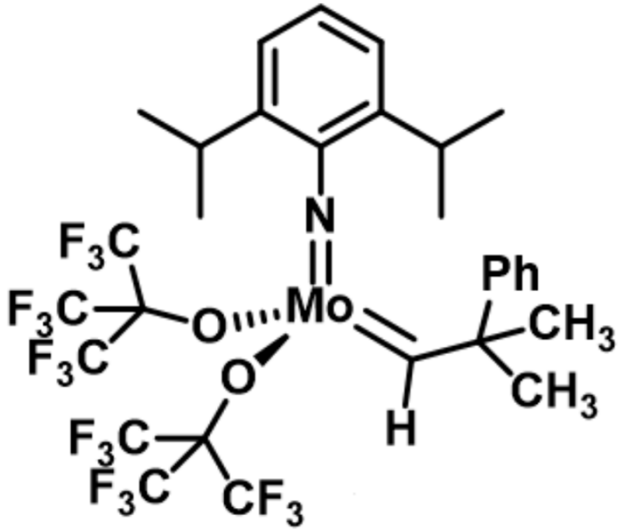
PBE0(D3BJ)/def2tzvpp

Grubbs, R. et al. *Tetrahedron Lett.* **2000**, *41*, 4689.

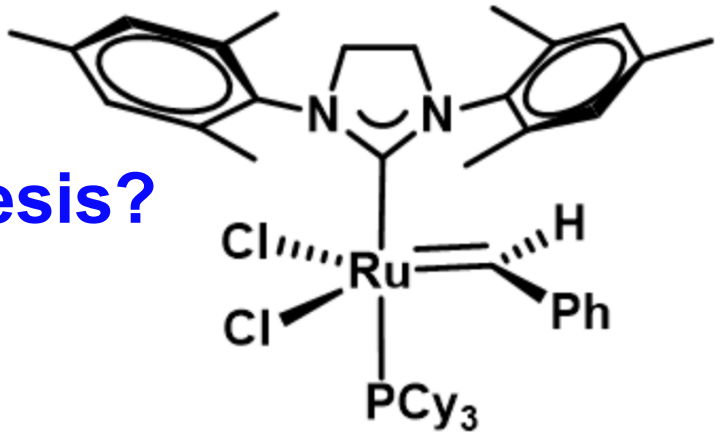
Comparing Schrock & Grubbs Cat.

- More Reactive
- **Nucleophilic** Mo=C Bond
- **Polarized** Carbene: $^{\delta+}$Mo=C$^{\delta-}$
- Ring Formation Determining
- **Hard** Metal-Center

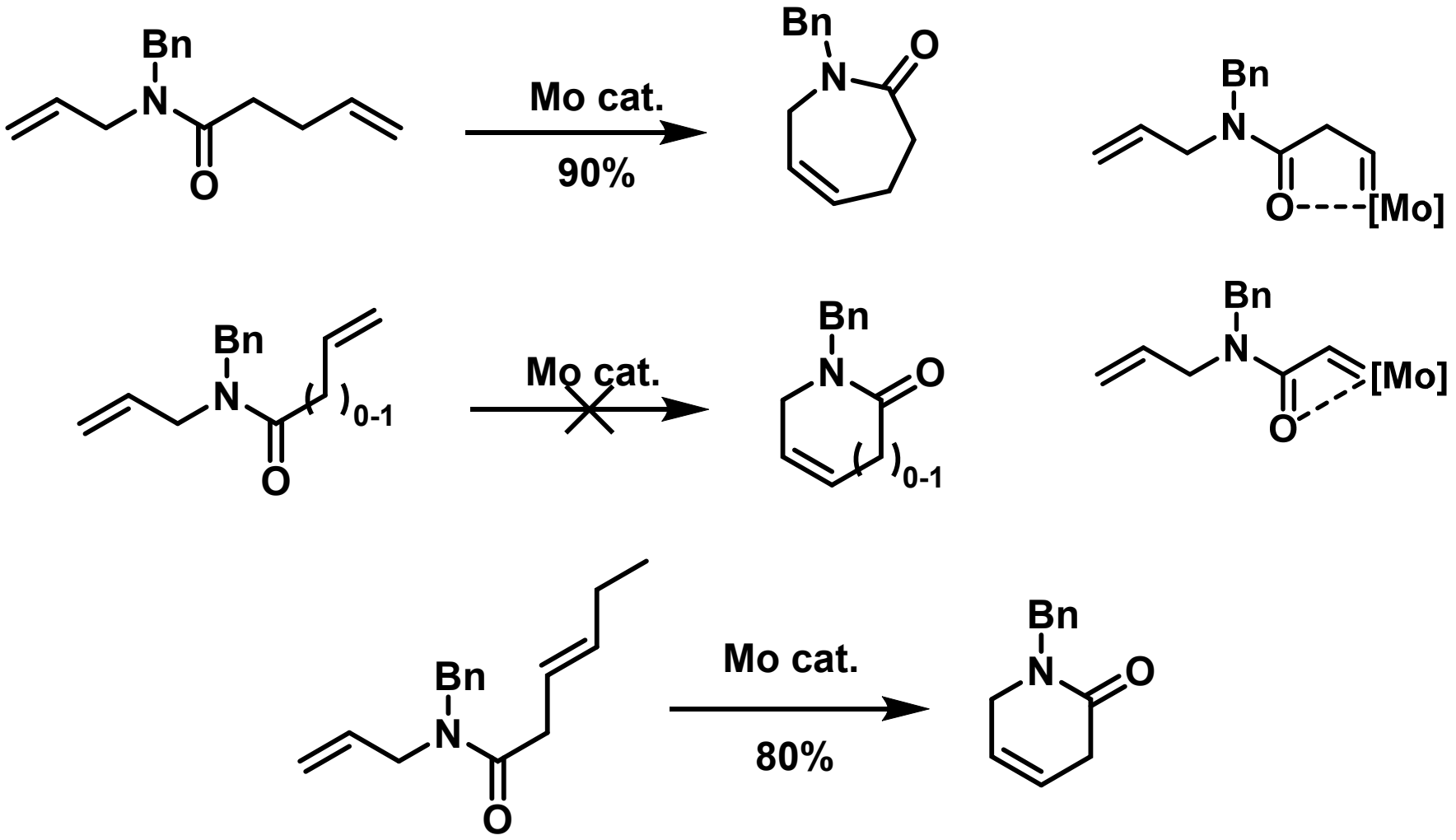
- More Stable
- **Electrophilic** Ru=C Bond?
- **Polarized** Carbene: $^{\delta-}$Ru=C$^{\delta+}$
- Coordination & Ring Formation
- **Soft** Metal-Center



Effect on Metathesis?



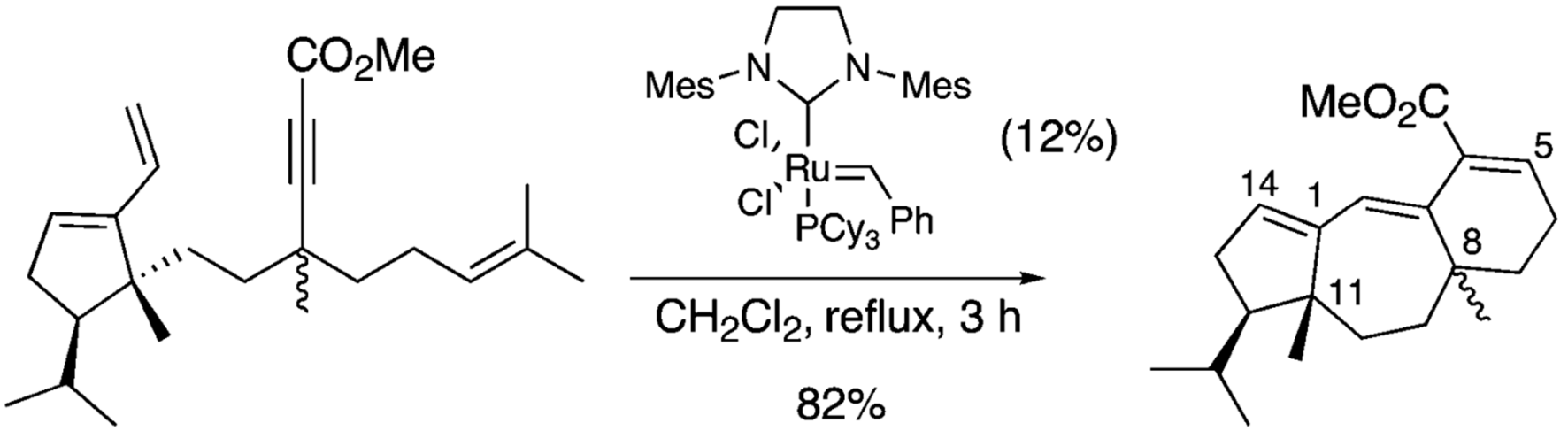
Schrock RCM: Killed by Coordination



Grubbs, R. et al. *J. Am. Chem. Soc.* **1992**, *114*, 7324.

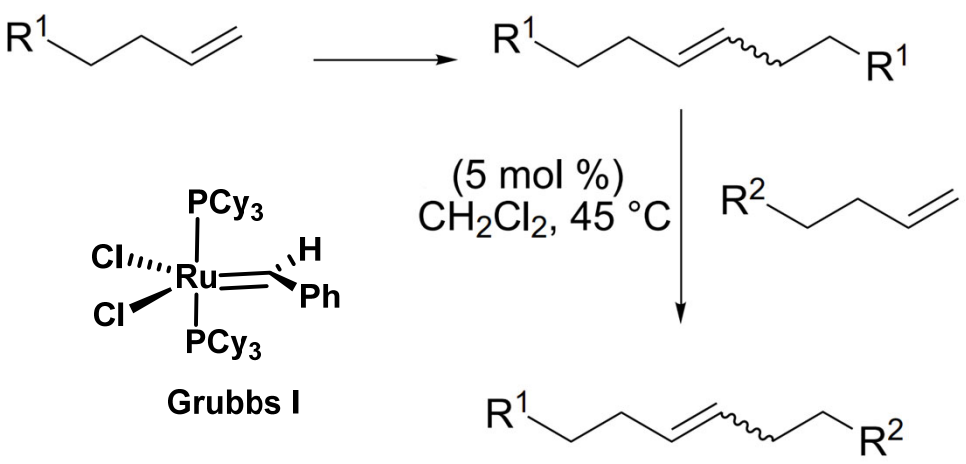
Grubbs RCM: Well Developed

- Functional Groups Tolerance
- **Reactivity** & **Regioselectivity** **NOT** Very Important
- **Stereoselectivity** Controlled by Substrates
- Various RCM Strategies in Total Synthesis

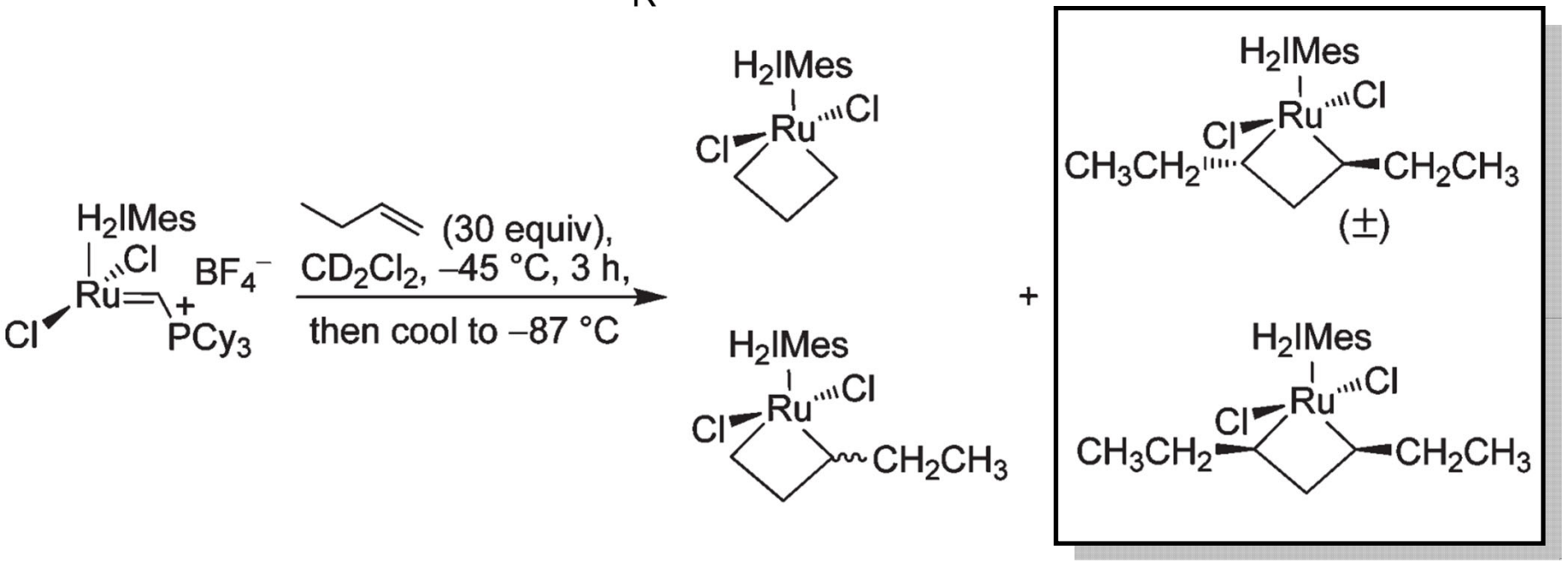


Richard, L. et al. *Org. Lett.* **2004**, *6*, 1817.

Grubbs CM: Early Stage

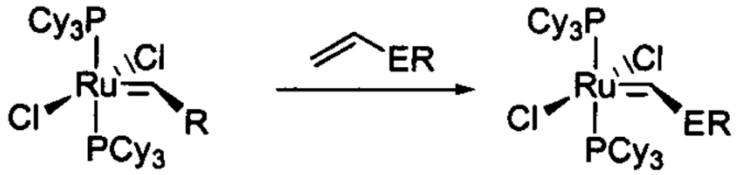


- **Cross** vs. **Self**
- α,α': **Non-Productive**
- **"Excess"** Strategy
- Alkene-Steric-Determination
- **Distinguishable** Alkenes?



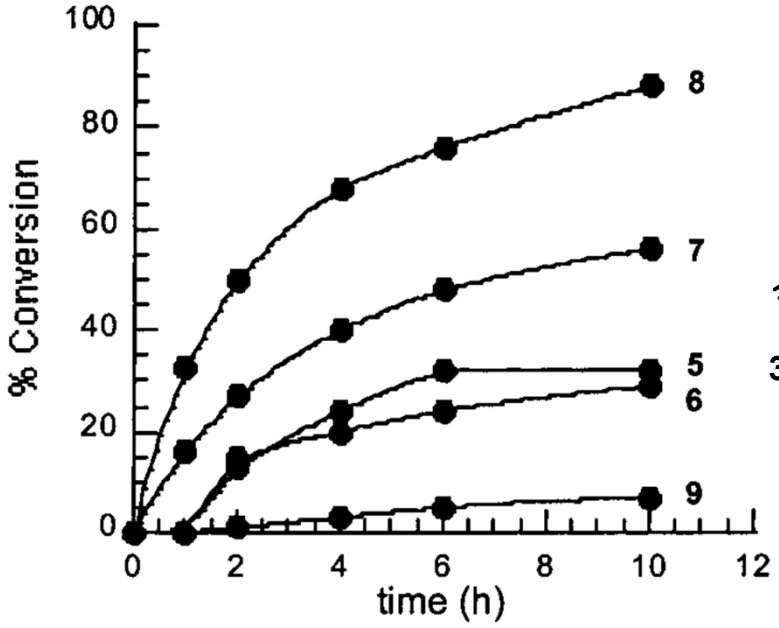
Blechert, S. et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.; Grubbs, R. et al. *J. Am. Chem. Soc.* **2011**, *133*, 6429.

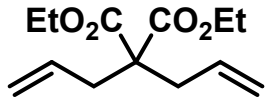
Grubbs I CM: Restrictions & New Cat.



R = Ph (**1a**)
R = $CHC(CH_3)_2$ (**1b**)

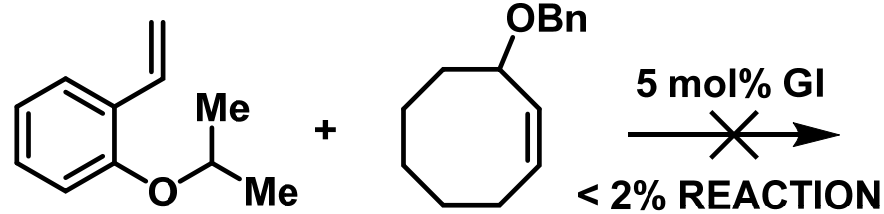
5 ER = OCH_2CH_3, 66%
6 ER = SCH_2CH_3, 71%
7 ER = SPh, 87%
8 ER = N(carbazole), 77%
9 ER = N(pyrrolidinone), 86%

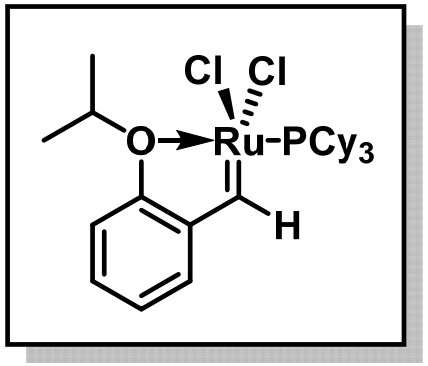




3 mol% cat., 60 °C

- Electron-Rich **First** but **Bad**
- EWA Restricted by k_1/k_{-1} & k_2
- EWA: Grubbs II Work
- Catalysts More Suitable?
- By **Accident**

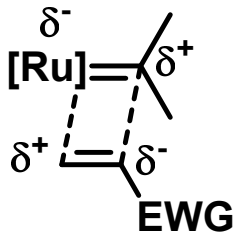




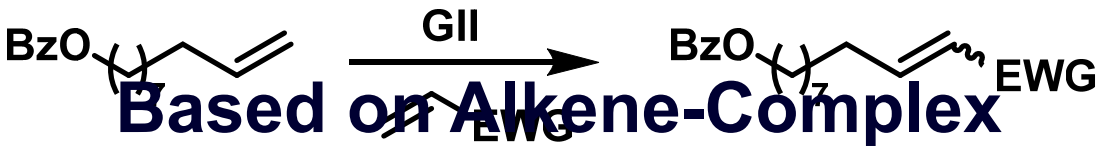
Grubbs, R. et al. *Organometallics* **2002**, *21*, 2153.; Hoveyda, A. et al. *J. Am. Chem. Soc.* **1998**, *120*, 2343.

Grubbs CM: E-W Alkenes

- Start from **Non**-Electron-Withdrawing Alkenes
- **Correct Regioselectivity**
- Ring Formation Prefer **EWG**
- **Late** but **Work!**

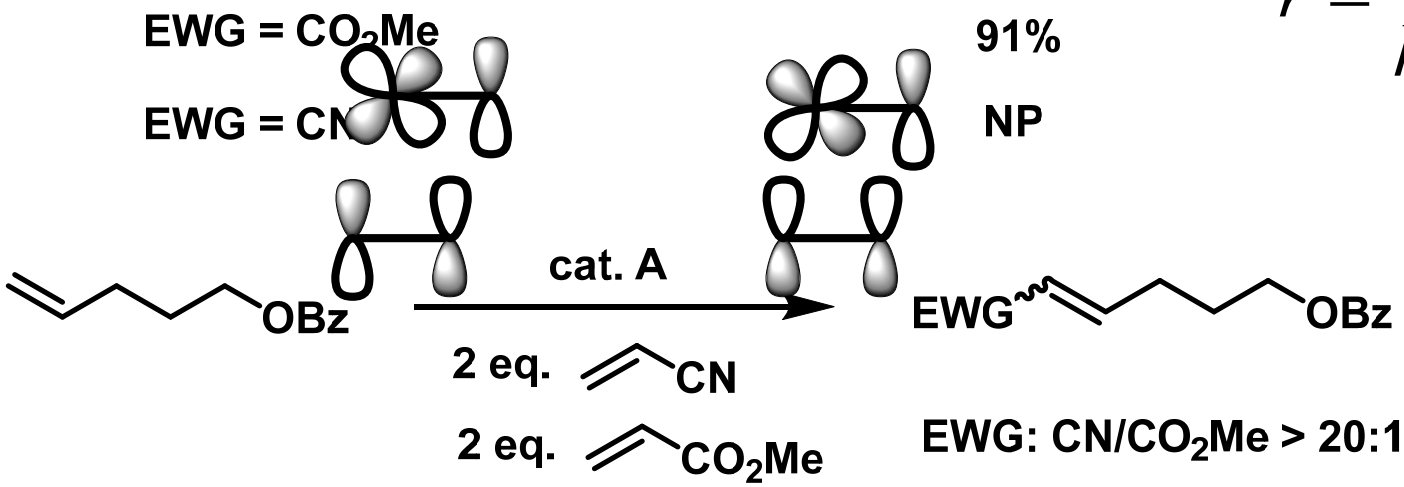


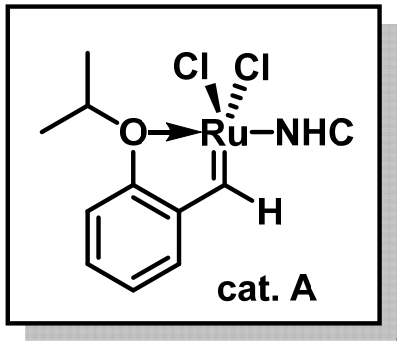
Cat. A vs. Grubbs II in RCM?



Based on Alkene-Complex

$$r = \frac{k_1 k_2 [\mathrm{RuP}][\mathrm{Alkene}]}{k_{-1}[\mathrm{P}] + k_2 [\mathrm{Alkene}]}$$

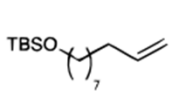
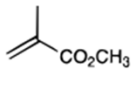
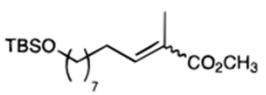
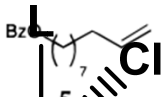
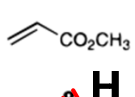
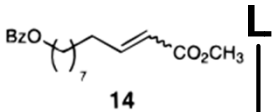
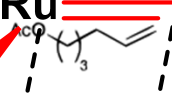
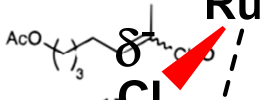
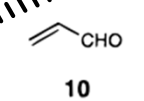
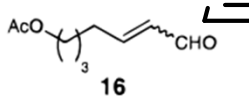
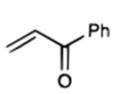
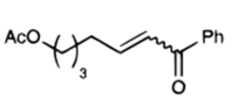
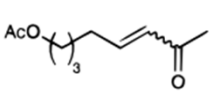


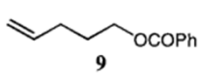
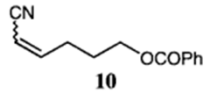
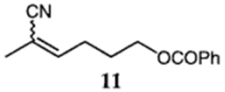
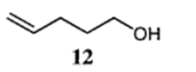
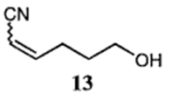
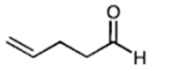
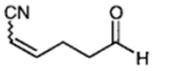
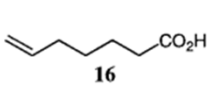
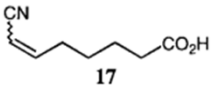
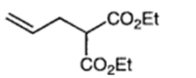
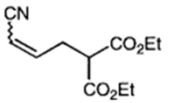
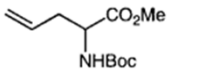
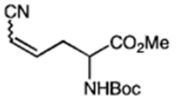
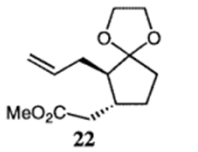
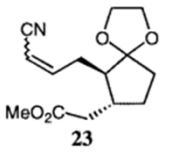
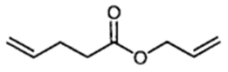
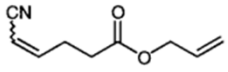


Grubbs, R. et al. *J. Am. Chem. Soc.* **2000**, *122*, 3783.; Blechert, S. et al. *Synlett* **2001**, *3*, 430.

Electron-Withdrawing Alkenes

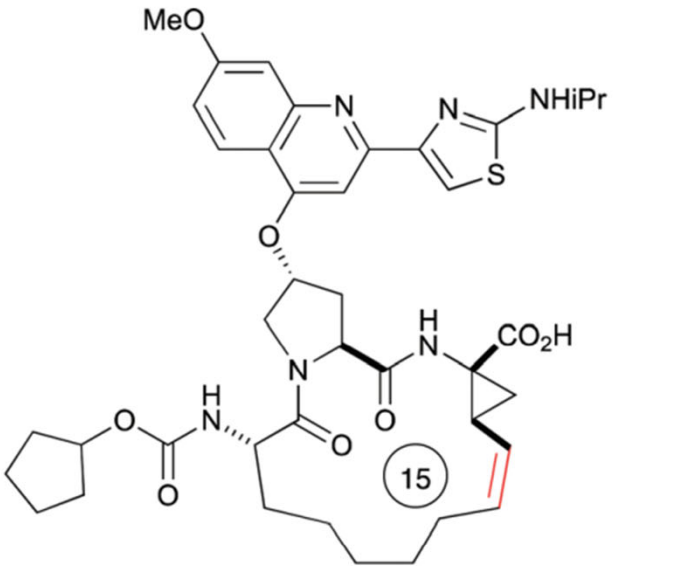
- Catalyzed by **Grubbs II** or **Cat. A**

entry	terminal olefin	α-functionalized olefin (equiv.)	product	isolated yield(%)	E/Z[b]
1	 4	 7 (0.5)	 13	62	>20:1
2	 5	 8 (2.0)	 14	91	4.5:1
3	 6	 9 (0.5)	 15	92	>2
4	6	 10 (2.0)	 16	62	1.1:1
5	6	 11 (2.0)	 17	99	>20:1
6	6	 12 (2.0)	 18	95	>20:1

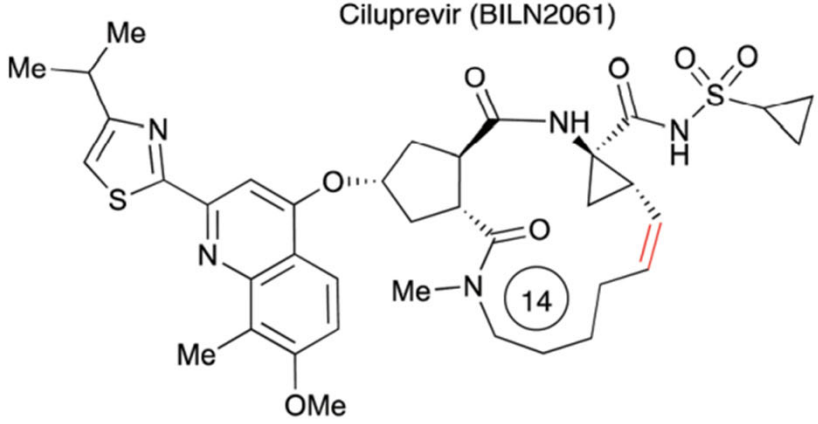
Substrate	Product	Yield (Z/E)
 9	 10	88 % (4:1)
	 11	68 % (2:1)[a]
 12	 13	81 % (3:1)
 14	 15	91 % (4:1)
 16	 17	76 % (3:1)
 18	 19	79 % (3:1)[b]
 20	 21	83 % (3:1)[b]
 22	 23	83 % (9:1)
 24	 25	60 % (4:1)[c]

Grubbs, R. et al. *J. Am. Chem. Soc.* **2000**, *122*, 3783.; Blechert, S. et al. *Synlett* **2001**, *3*, 430.

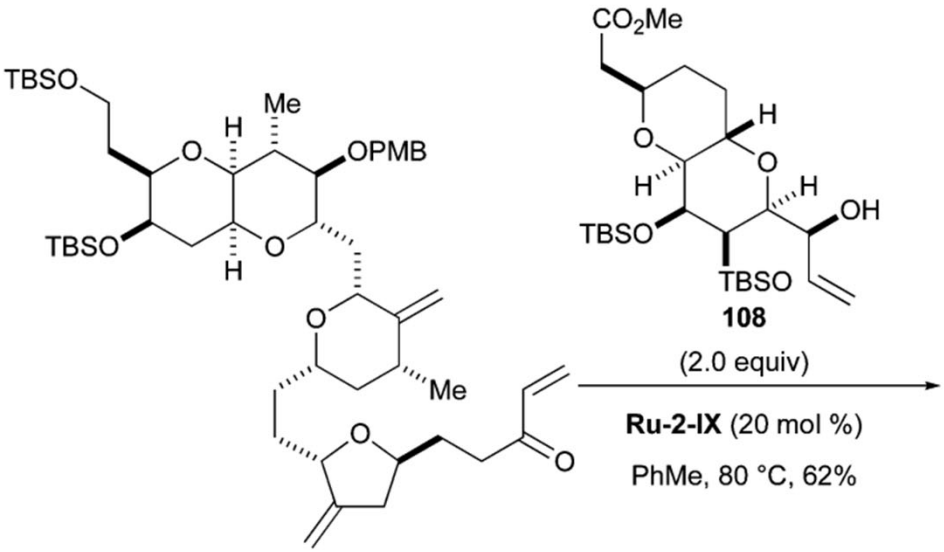
Grubbs CM in Total Synthesis

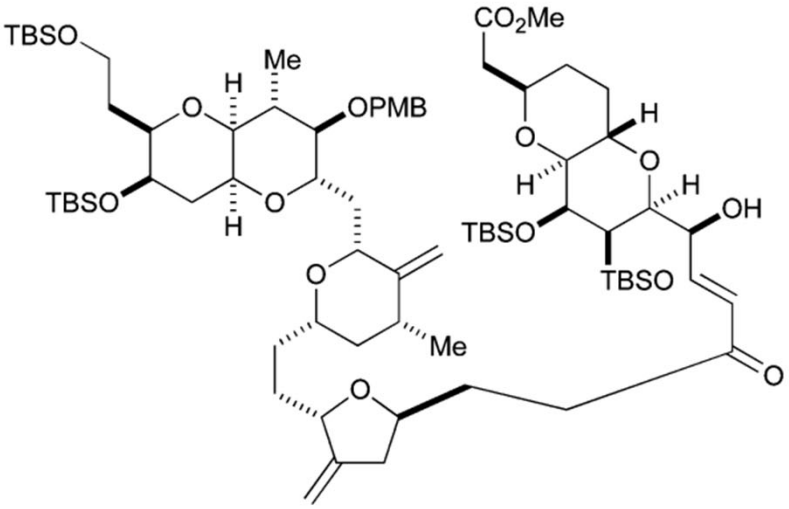


Ciluprevir (BILN2061)



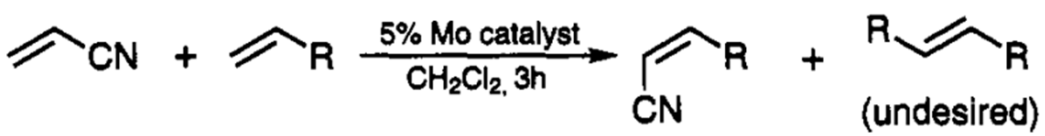
Simeprevir (TMC435, Olysio)





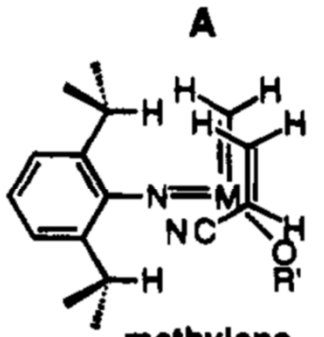
Blechert, S. et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.

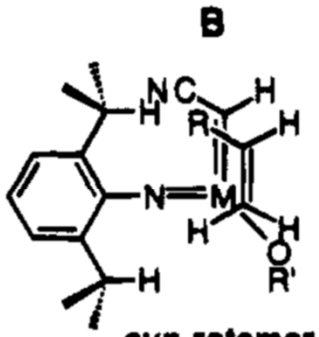
Schrock CM: Priority Inversion



entry	R	NCCH=CHR (%)	cis: trans[b]	RCH=CHR (%)
1	$(CH_2)_5CH_3$	56 (75)	9:1	4[b]
2	$(CH_2)_7CH_3$	72 (92)	8.5:1	4[b]
3	$(CH_2)_3Br$	45	7.3:1	11[b]
4	$(CH_2)_2Br$	17.5	9:1	20[b]
5	$(CH_2)_4OBn$	77	9:1	0[c]
6	$(CH_2)_3OBn$	60	7.6:1	<1[c]
7	$(CH_2)_2OBn$	40	4:1	0[c]
8	$(CH_2)_4OTBS$	90	6.7:1	7[c]
9	$(CH_2)_3OTBS$	68	5.6:1	0[c]
10	$(CH_2)_2OTBS$	73	5.3:1	10[c]
11	CH_2TMS	76	3:1	0[b]
12	*o*-$MeOC_5H_4CH_2$	72	9:1	9[b]
13	$(CH_2)_6CH=CH_2$	53[d]	8:1	19[b]
14	$(CH_2)_2C(O)OBn$	44	5.6:1	6[b]
15	$(CH_2)_3CH(OMe)_2$	79	7:1	11[b]
16	$CH_2CMe_2CH_2CH(OMe)_2$	64[e]	3:1	0[b]

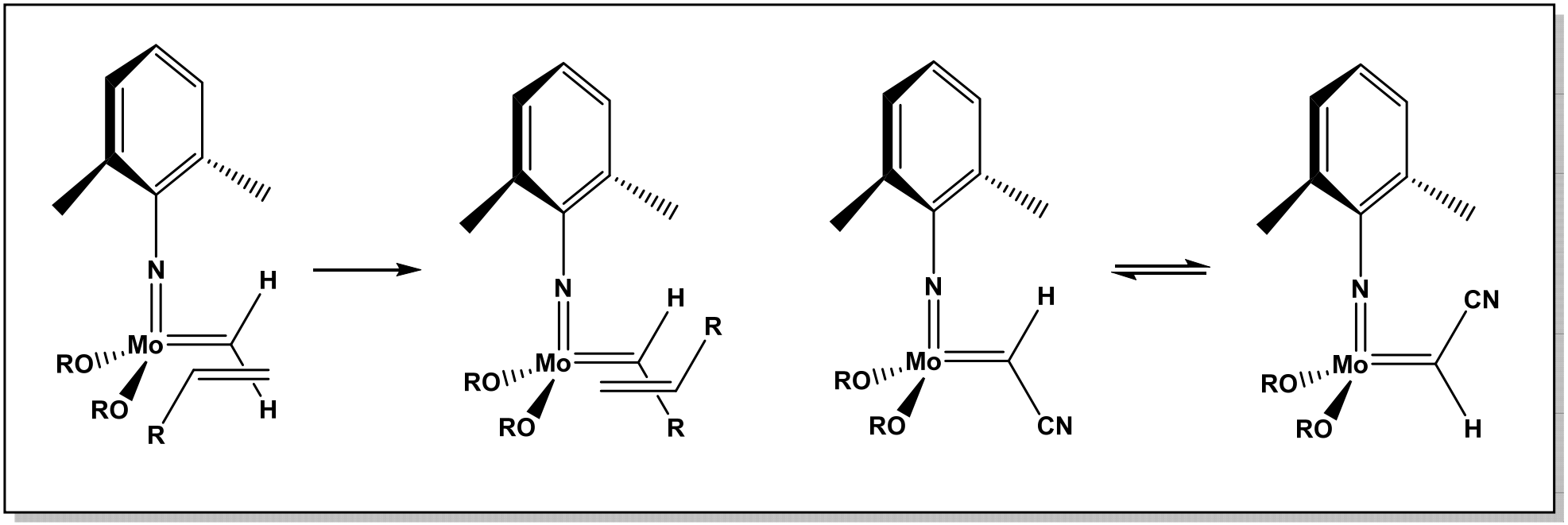
- EWG Faster
- Active EWG Carbene
- **Rate** vs. **Regio**
- E-D Alkenes Work!
- **Stereo-Improve?**





Goldberg, D. et al. *J. Am. Chem. Soc.* **1995**, *117*, 5162.

Schrock CM: Selectivity Explain

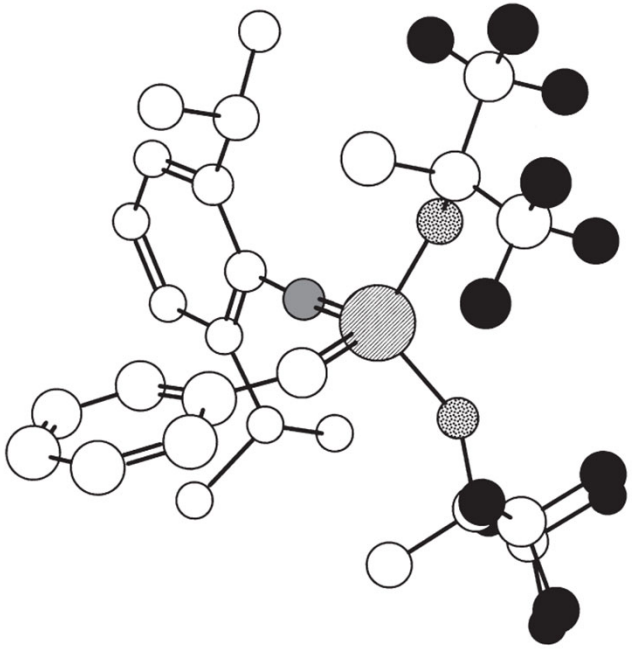


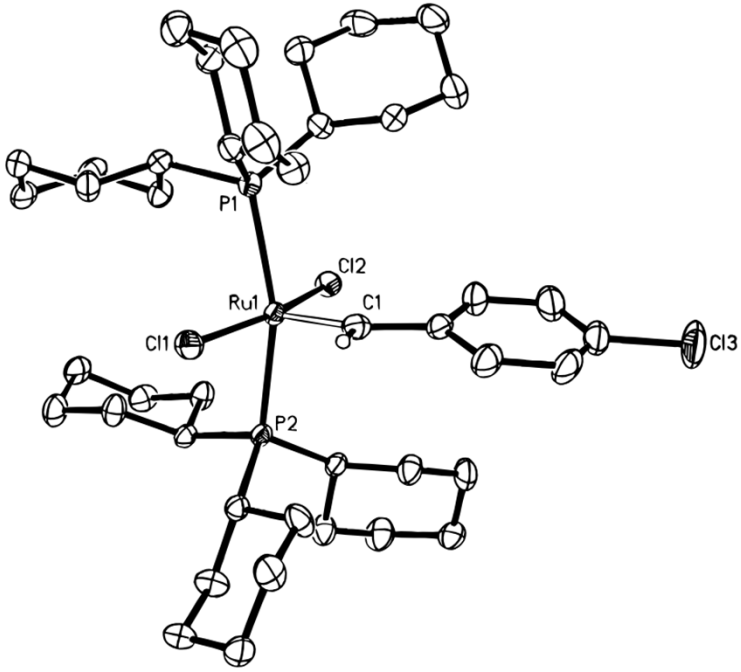
Outline

- **Introduction**
- **Classical Catalysts System**
  Schrock Catalysts
  Grubbs Catalysts
  RCM Reaction
  Classical CM Reaction
- **Catalysts Improvement**
  Restrictions of Classical Catalysts
  Solutions of Grubbs Catalysts
  Solutions of Schrock Catalysts
- **Summary**
- **Acknowledgement**

Restrictions of Classical Catalysts

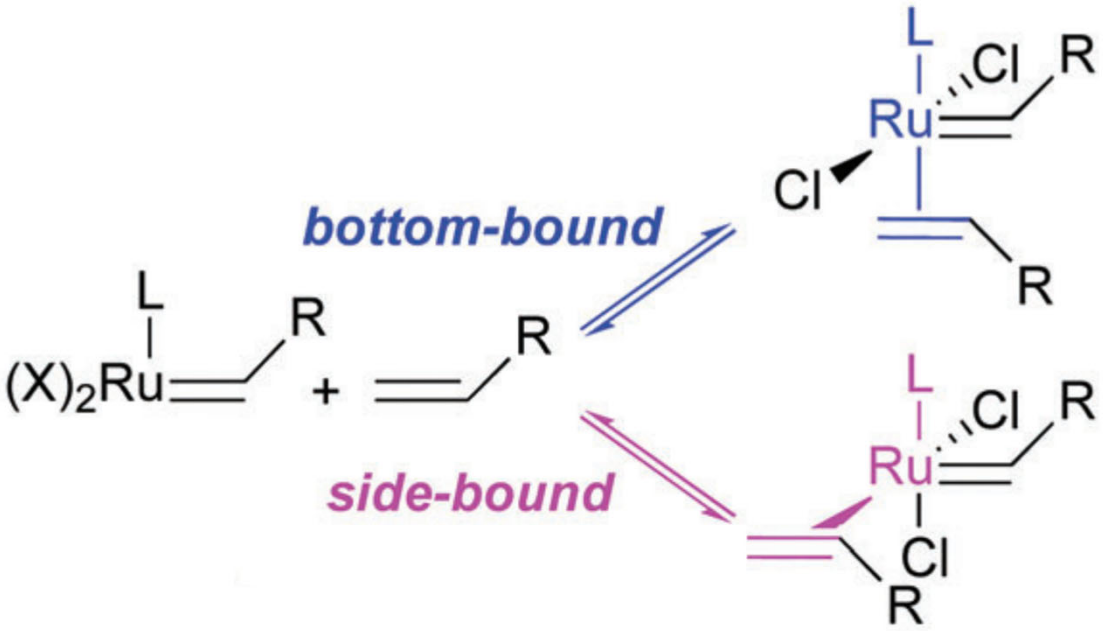
- Stereoselectivity Controlled by Alkenes Rather than Catalysts.
- Multi-Substituted & Functionalized Alkenes?
- **Types of Catalysts** & **Types of Problems**?
- Make the Best of the Both Worlds?

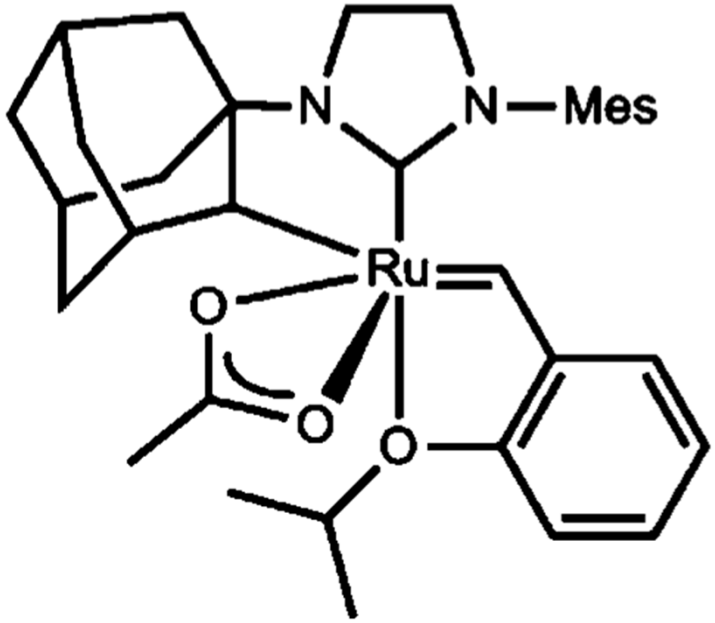




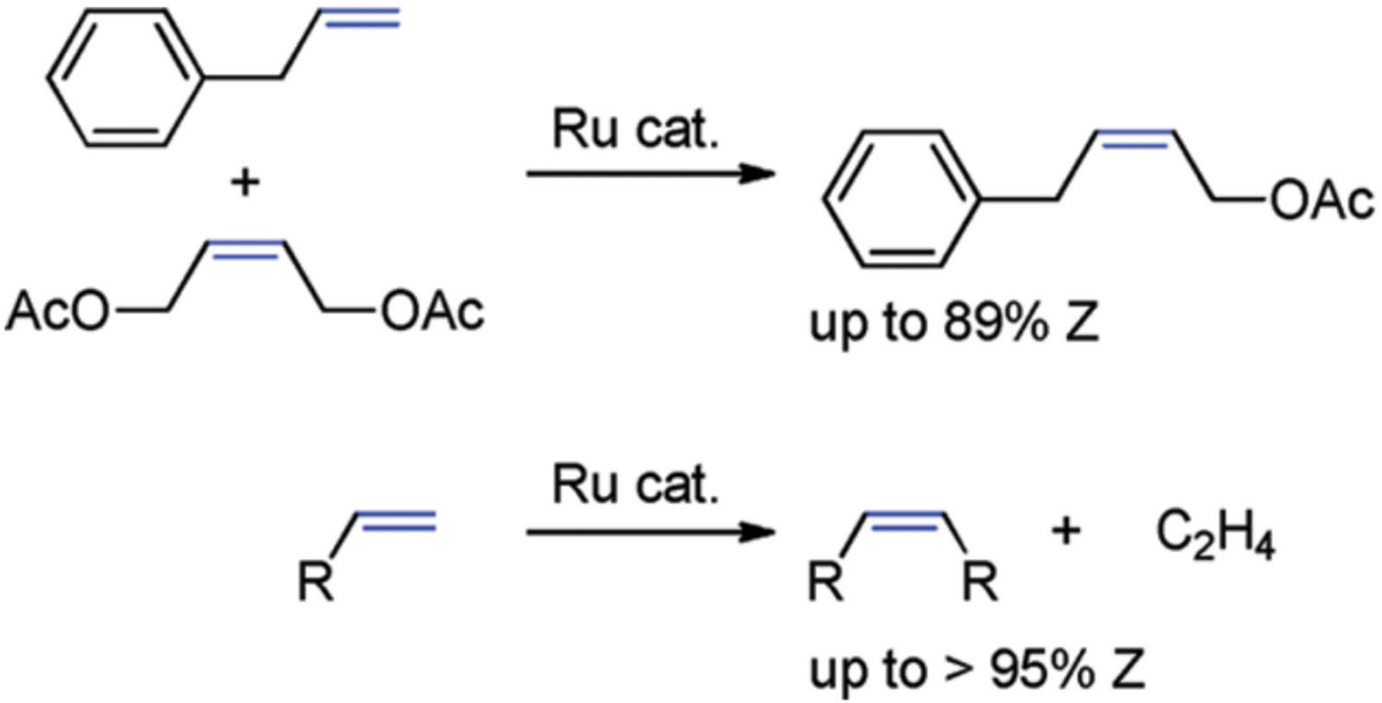
Grubbs: Change Attacking Direction

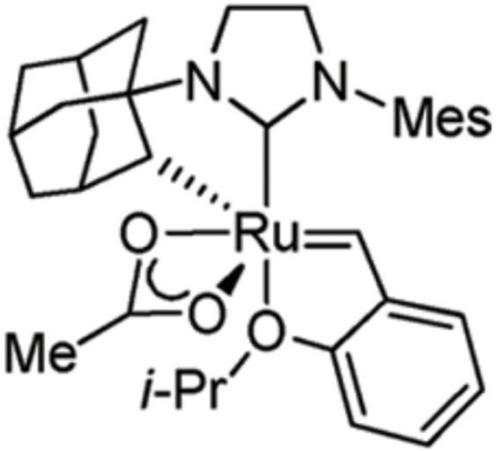
- Normally: ***Bottom-Bound*** Favored
- ***Side-Bound*** leads to ***Asymmetric***
- **Destroy Advantages?**
- **Turn Waste into Wealth?**





Grubbs III: *Z*-Selective Metathesis



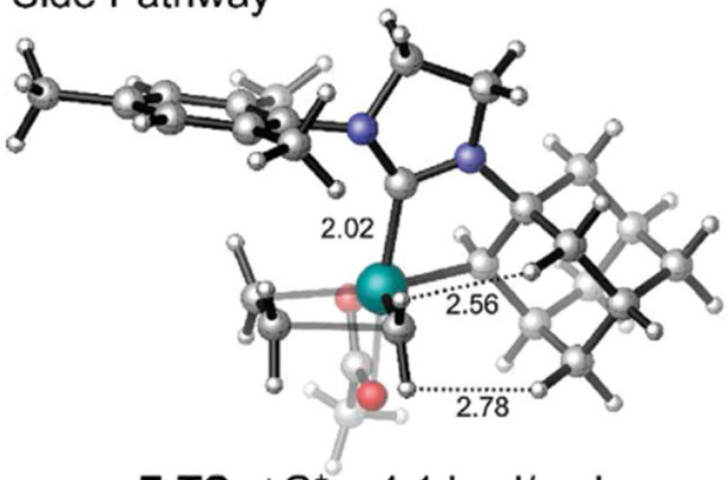


1

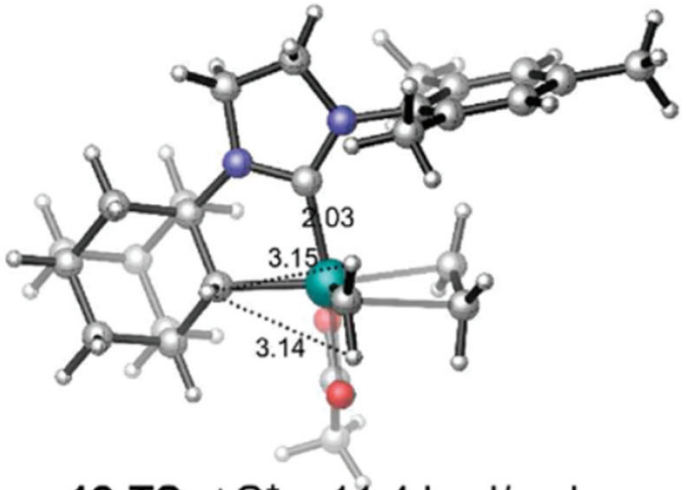
Grubbs, R. et al. *J. Am. Chem. Soc.* **2012**, *134*, 693.

Z-Selective Mechanism: Theoretical

Side Pathway

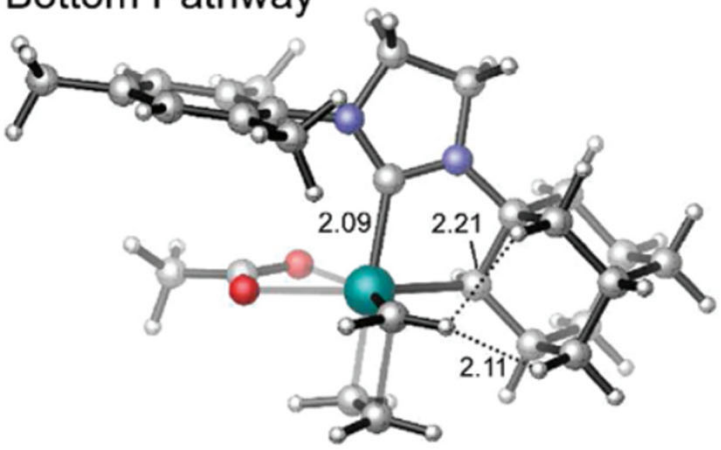


7-TS, $\Delta G^{\ddagger}$ = 4.1 kcal/mol

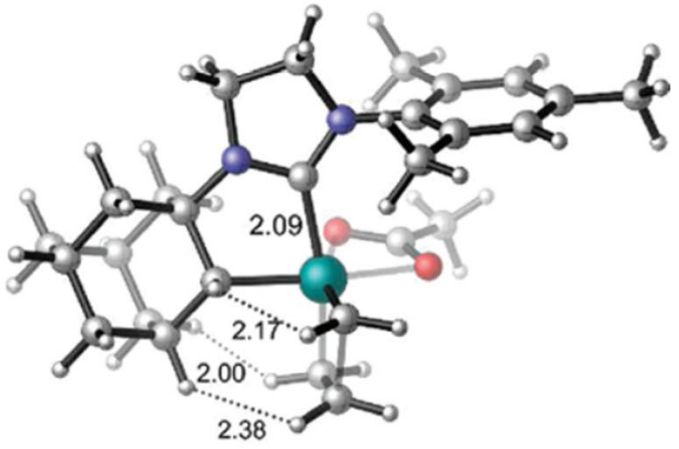


12-TS, $\Delta G^{\ddagger}$ = 11.4 kcal/mol

Bottom Pathway



25-TS, $\Delta G^{\ddagger}$ = 14.5 kcal/mol

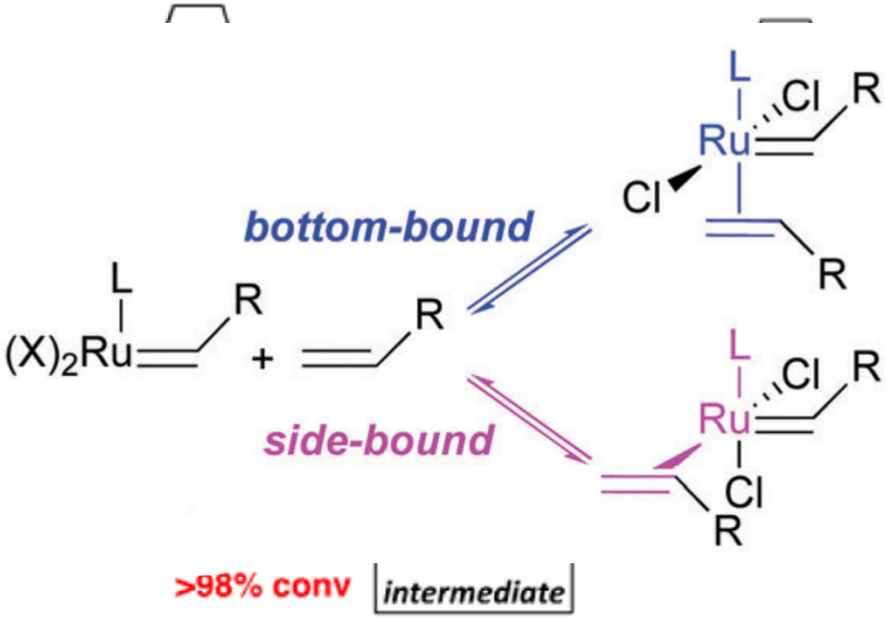


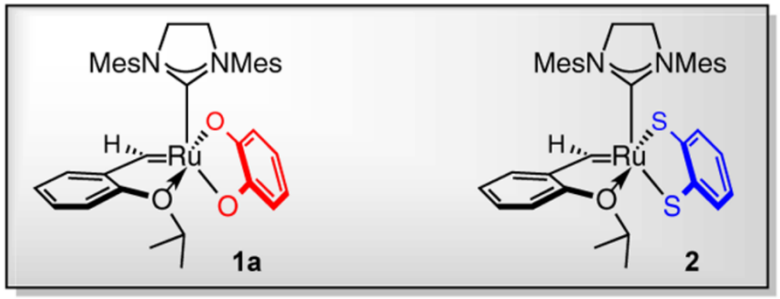
28-TS, $\Delta G^{\ddagger}$ = 13.5 kcal/mol

Houk, K. et al. *J. Am. Chem. Soc.* **2012**, *134*, 1464.

Hoveyda: Restricting Bond Angle

- ***Side-Bound*** Only
- **Oxygen** vs. **Sulfur**
- Stereoselectivity
- Tolerance

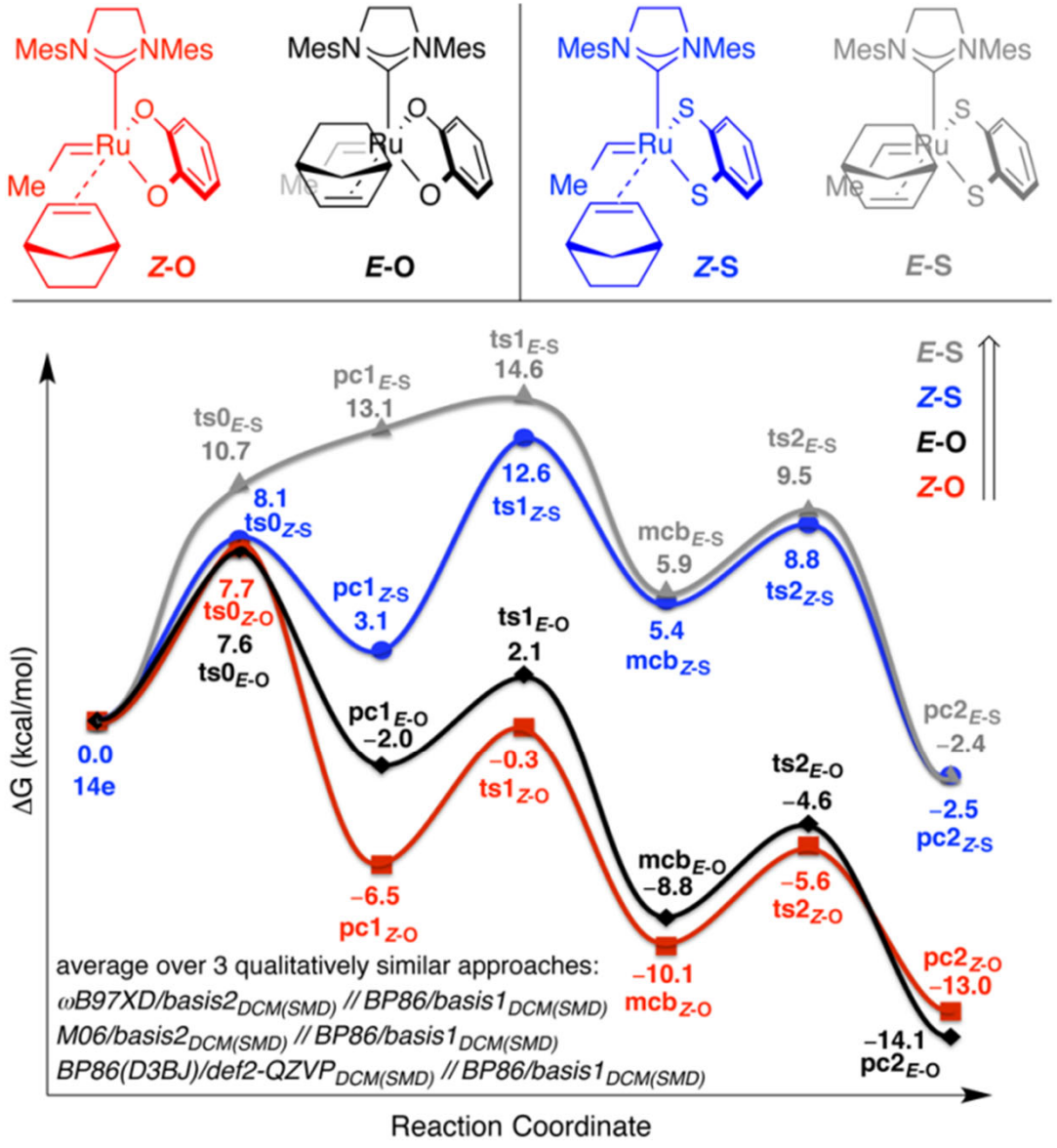




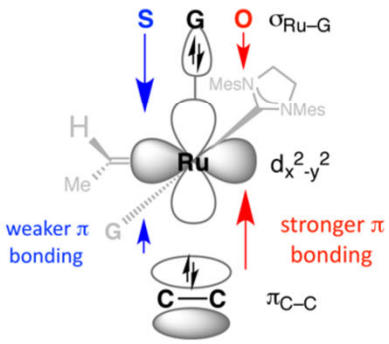
entry	product	R	with 1a conv (%);[b] Z:E;[b]	with 2 conv (%);[b] Z:E;[b]
1	3	**a** C_6H_5	>98; 55:45[c]	>98; 97:3
2		**b** CH_2OH	<2; na	>98; 88:12
3		**c** $(CH_2)_2OH$	<2; na	>98; 87:13
4	4	**a** C_6H_5	<2; na	>98; 97:3
5		**b** C_6H_{11}	<2; na	88; >98:2

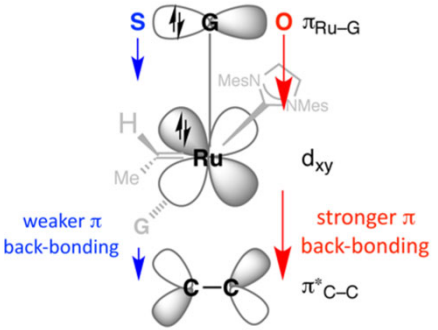
Hoveyda, A. et al. *J. Am. Chem. Soc.* **2014**, *136*, 14337.

Theoretical Study: O vs. S



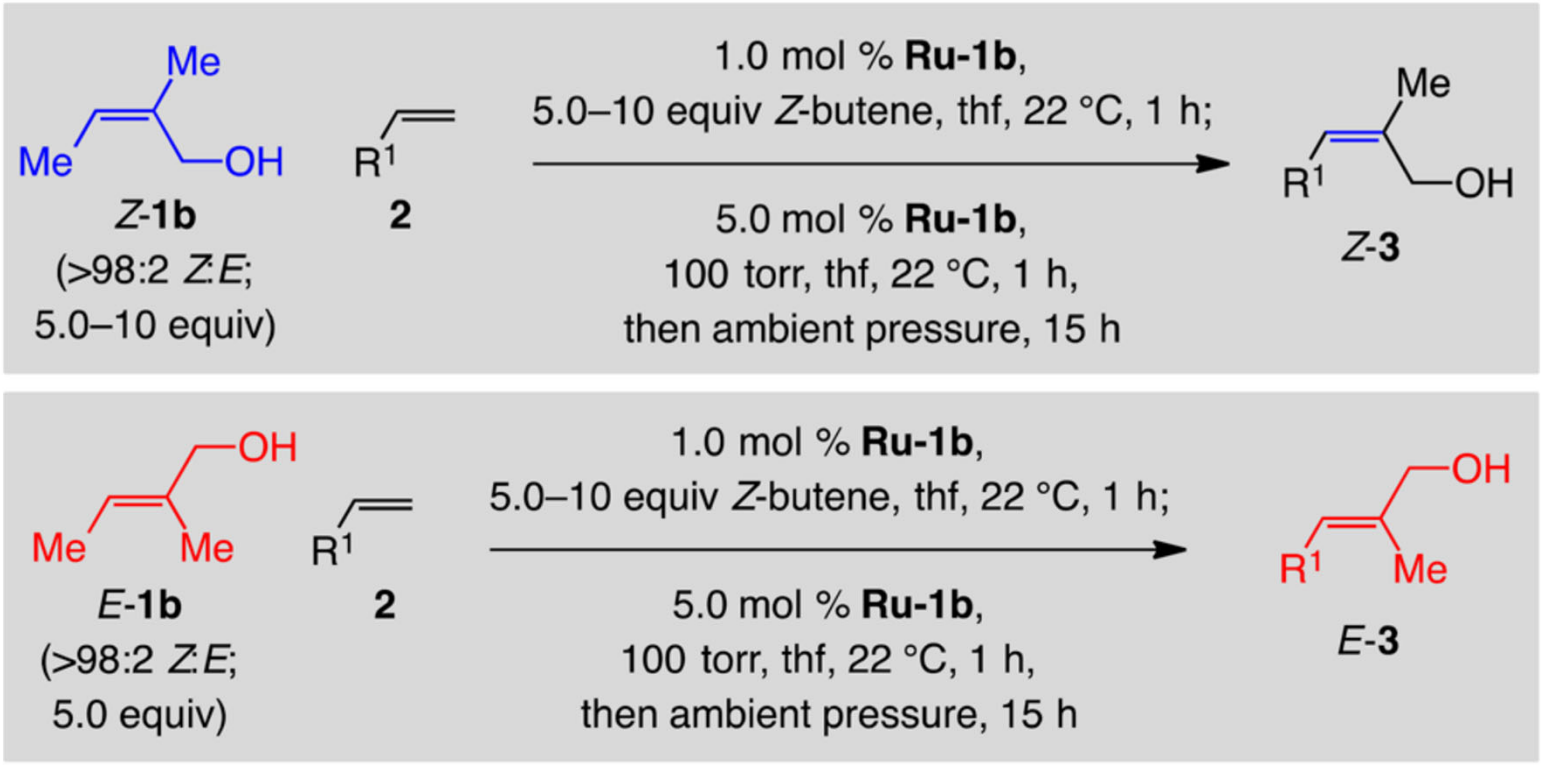
- **O**: Over Stable PC
- **S**: Ring-Forming RDS
- **Steric-Sensitive Step!**
- Similar to **Cat. A**
- E-W Alkenes First?
- **Steric but E-W Alkene?**

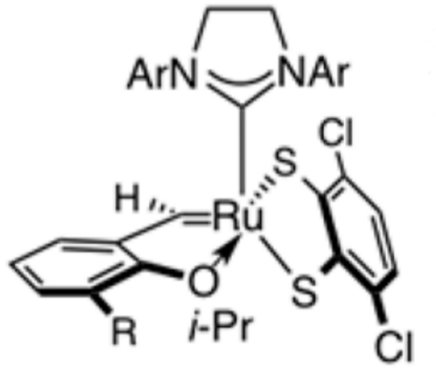




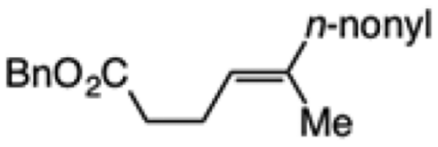
Hoveyda, A. et al. *J. Am. Chem. Soc.* **2014**, *136*, 14337.

Z-/*E*-Trisubstituted Allylic Alcohols



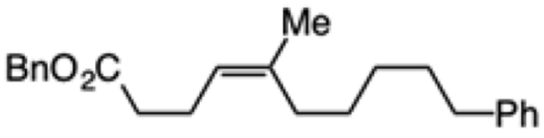


Ar = 2-F,6-Me-C_6H_3; R = H



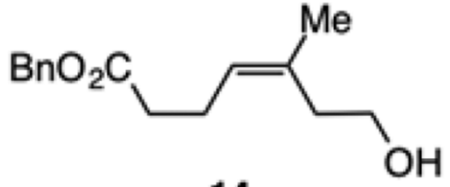
16

70% conv, <5% yield



15

79% conv, <5% yield

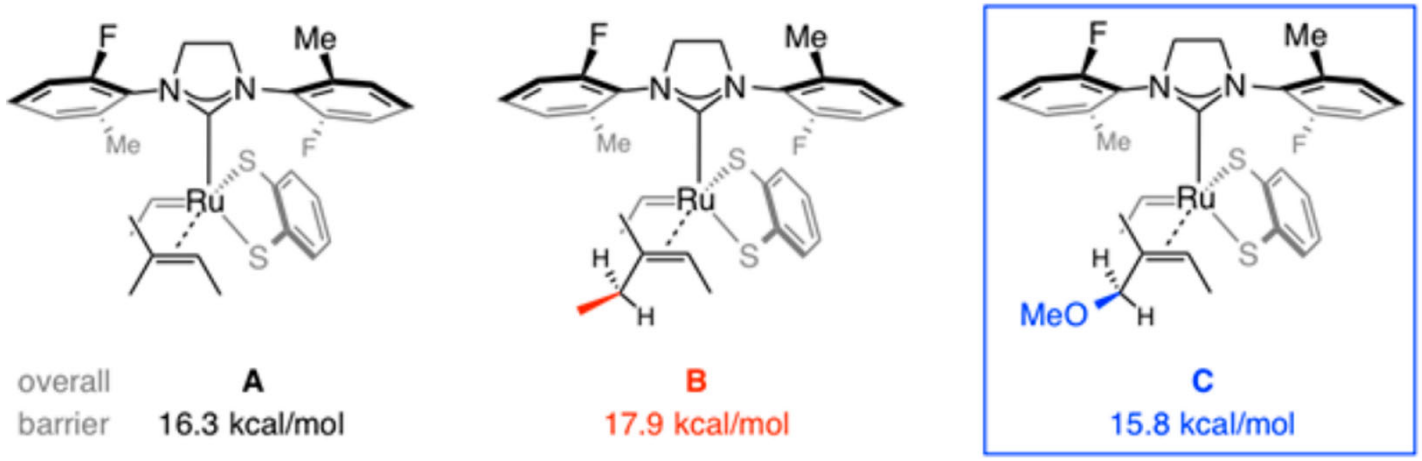


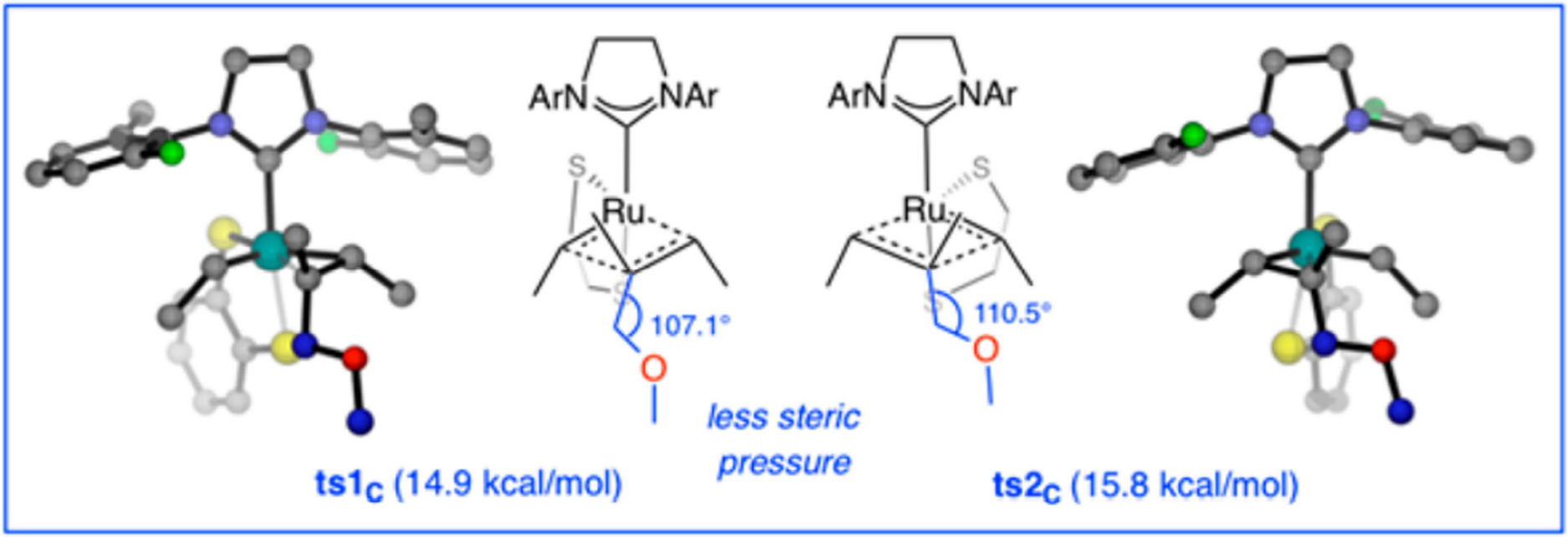
14

83% conv, <5% yield

Hoveyda, A. et al. *J. Am. Chem. Soc.* **2017**, *139*, 15640.

Steric Hindrance but E-W Alkenes

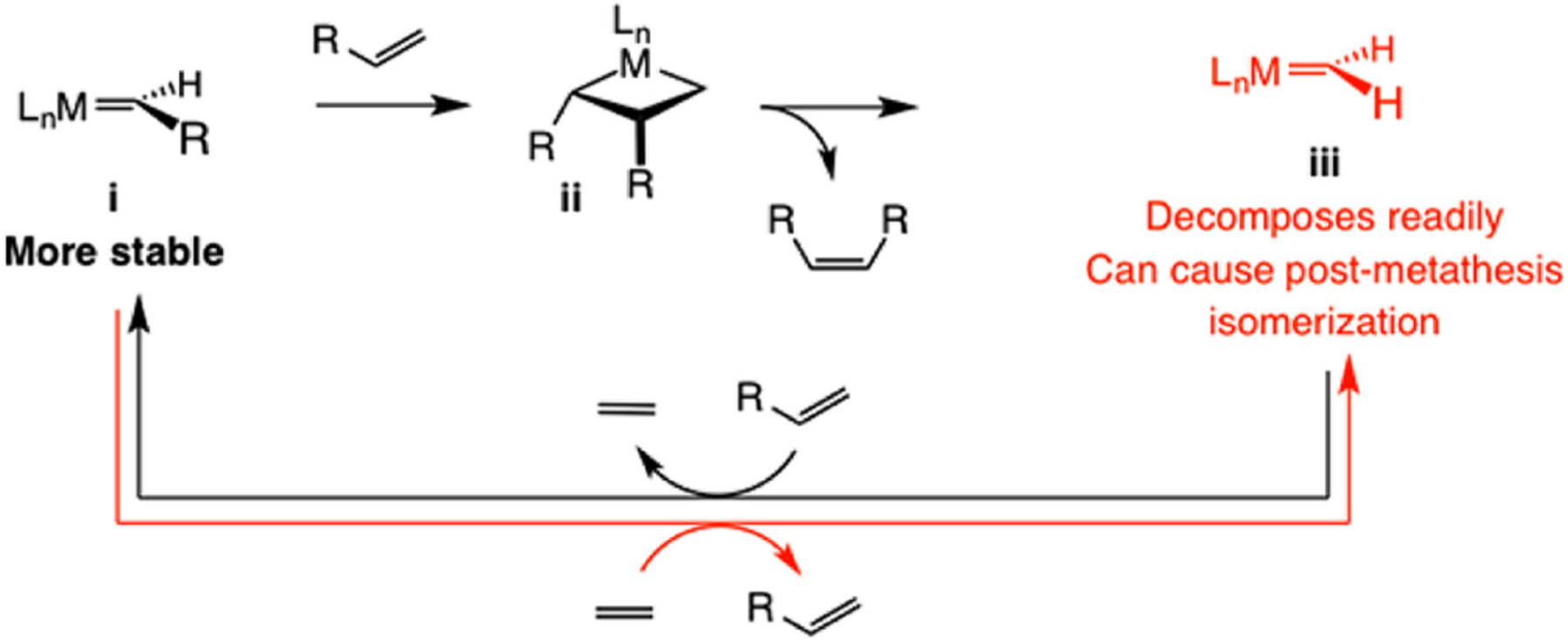




Hoveyda, A. et al. *J. Am. Chem. Soc.* **2017**, *139*, 15640.

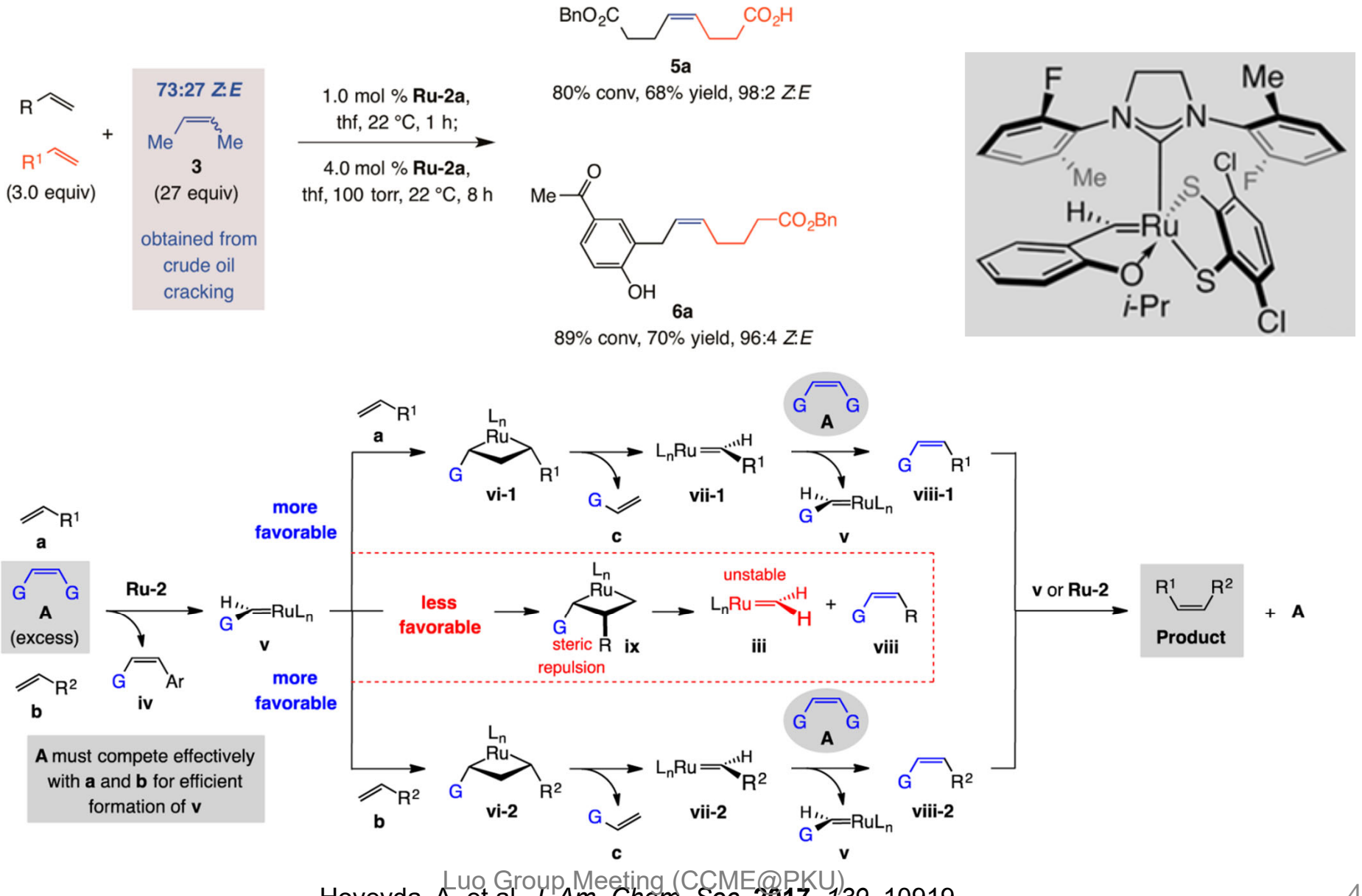
Challenge: Unstable Methylene-Carbene

"However, we have shown that the corresponding methylidene complexes are too unstable (partly due to 1,2-shift of the sulfide trans to the NHC to the carbene carbon),and thus reactions with terminal olefins are typically inefficient (i.e., ≤10% conversion)."



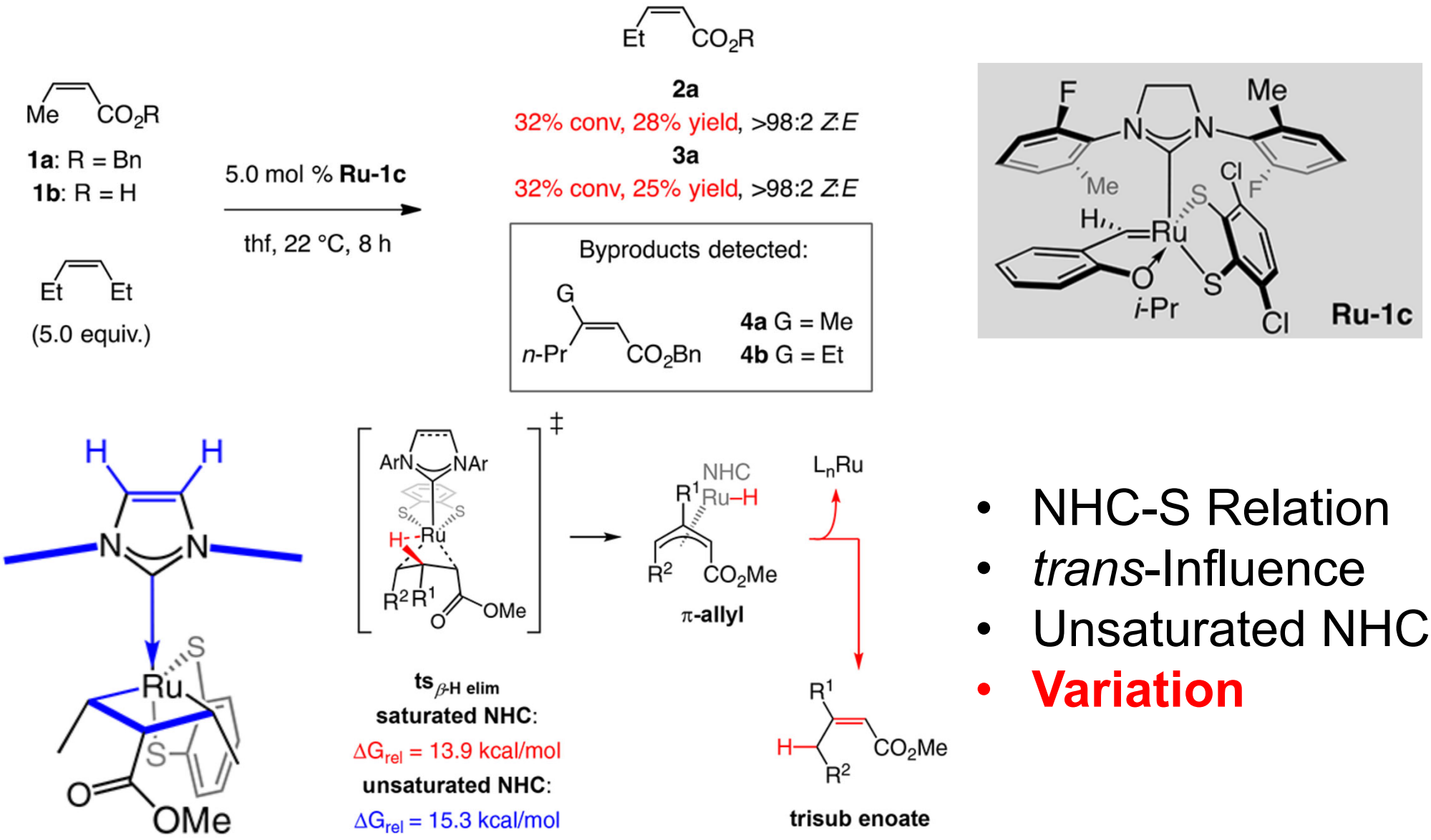
Hoveyda, A. et al. *J. Am. Chem. Soc.* **2017**, *139*, 10919.

Solution: In Situ Methylene Capping



Hoveyda, A. et al. *J. Am. Chem. Soc.* **2017**, *139*, 10919.

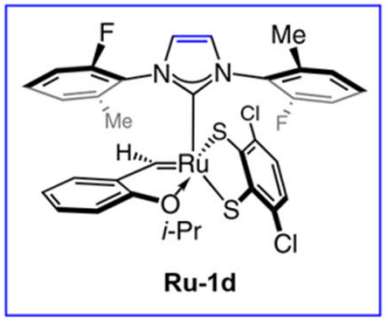
Classical E-W Alkenes: Elimination



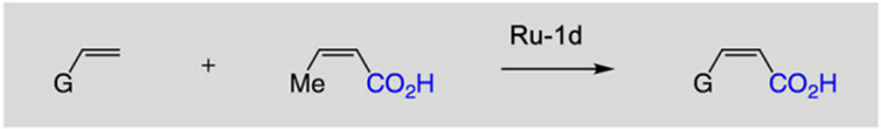
- NHC-S Relation
- *trans*-Influence
- Unsaturated NHC
- **Variation**

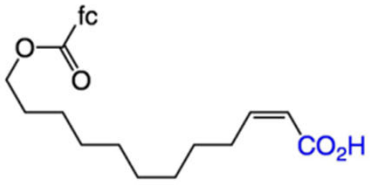
Hoveyda, A. et al. *J. Am. Chem. Soc.* **2019**, *141*, 7137.

Unsaturated NHCs Avoid Elimination



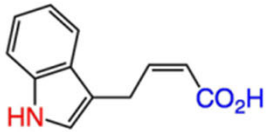
Ru-1d



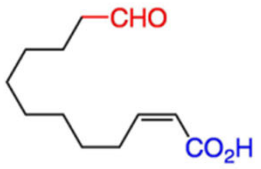


3b
Condition A:
60% conv, 33% yield,
>98:2 *Z*:*E*
Condition B:
89% conv, 52% yield,
>98:2 *Z*:*E*

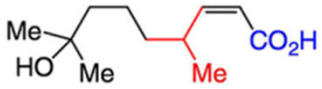
3c
Condition A:
65% conv, 41% yield,
>98:2 *Z*:*E*
Condition B:
92% conv, 65% yield,
>98:2 *Z*:*E*



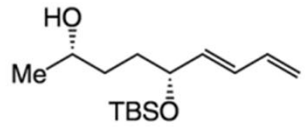
3d
Condition B:
86% conv, 52% yield,
>98:2 *Z*:*E*



3e
Condition B:
86% conv, 49% yield,
>98:2 *Z*:*E*

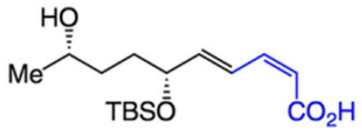


3f
Condition C:
66% conv, 63% yield,
98:2 *Z*:*E*



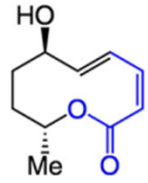
11
Prepared in 7 steps, 28% overall yield
from comm avail materials

Condition D



3g
71% conv. 53% yield,
>98:2 *Z*:*E*

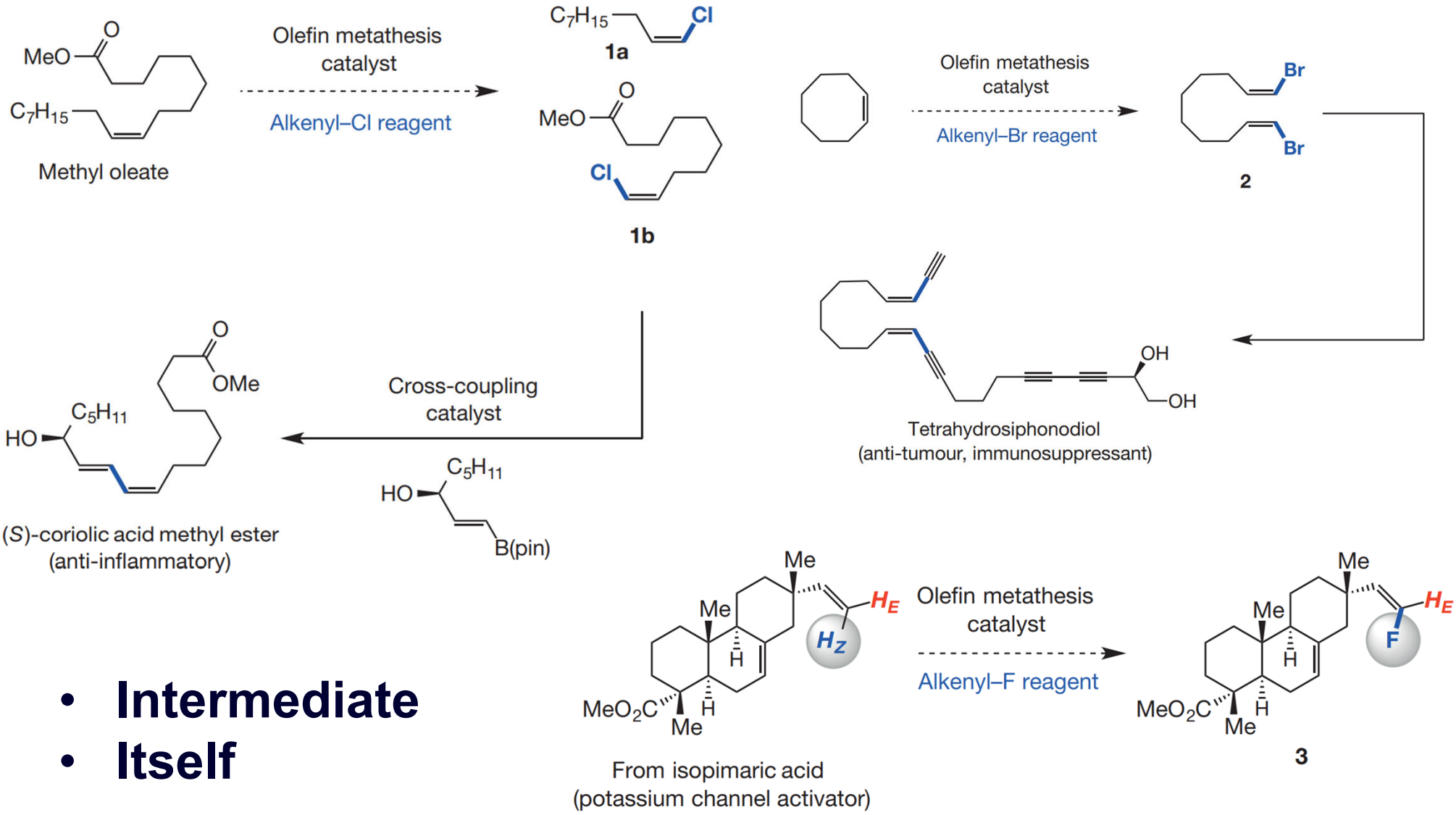
Ref. 14



stagonolide E

Hoveyda, A. et al. *J. Am. Chem. Soc.* **2019**, *141*, 7137.

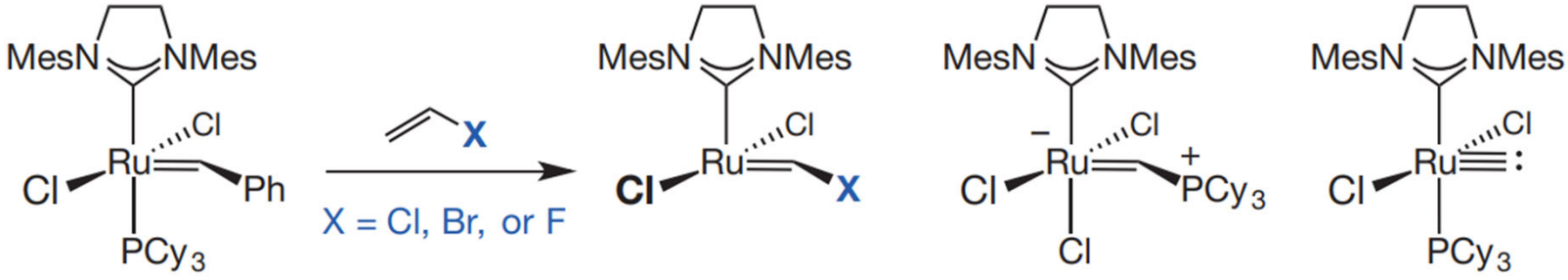
Any *Z*-Alkenes? Alkenyl-Halides

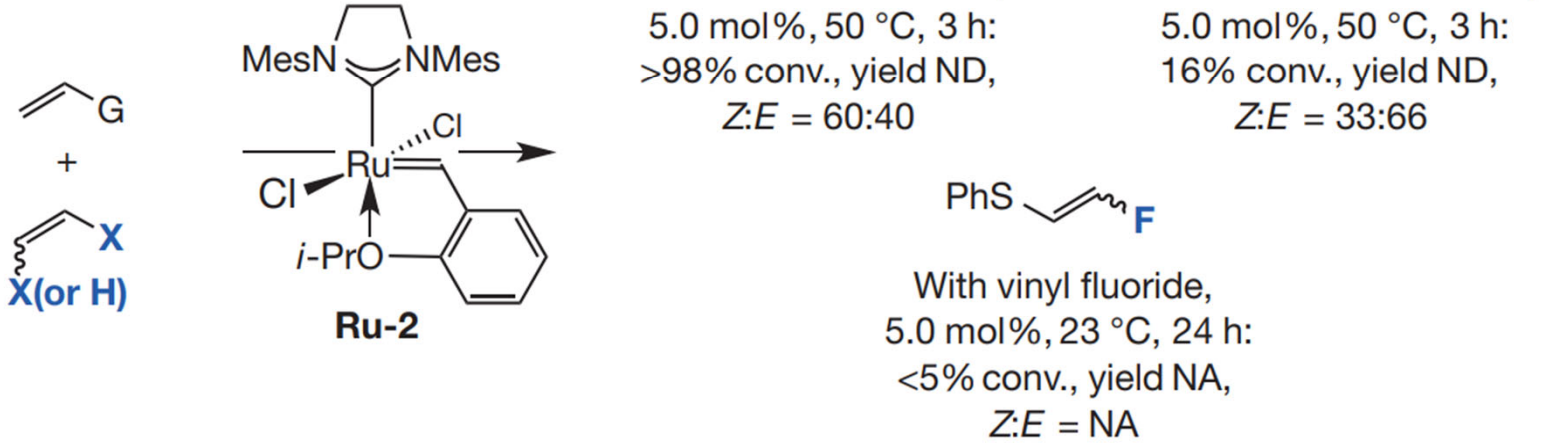


- **Intermediate**
- **Itself**

Hoveyda, A. et al. *Nature* **2016**, *531*, 459.

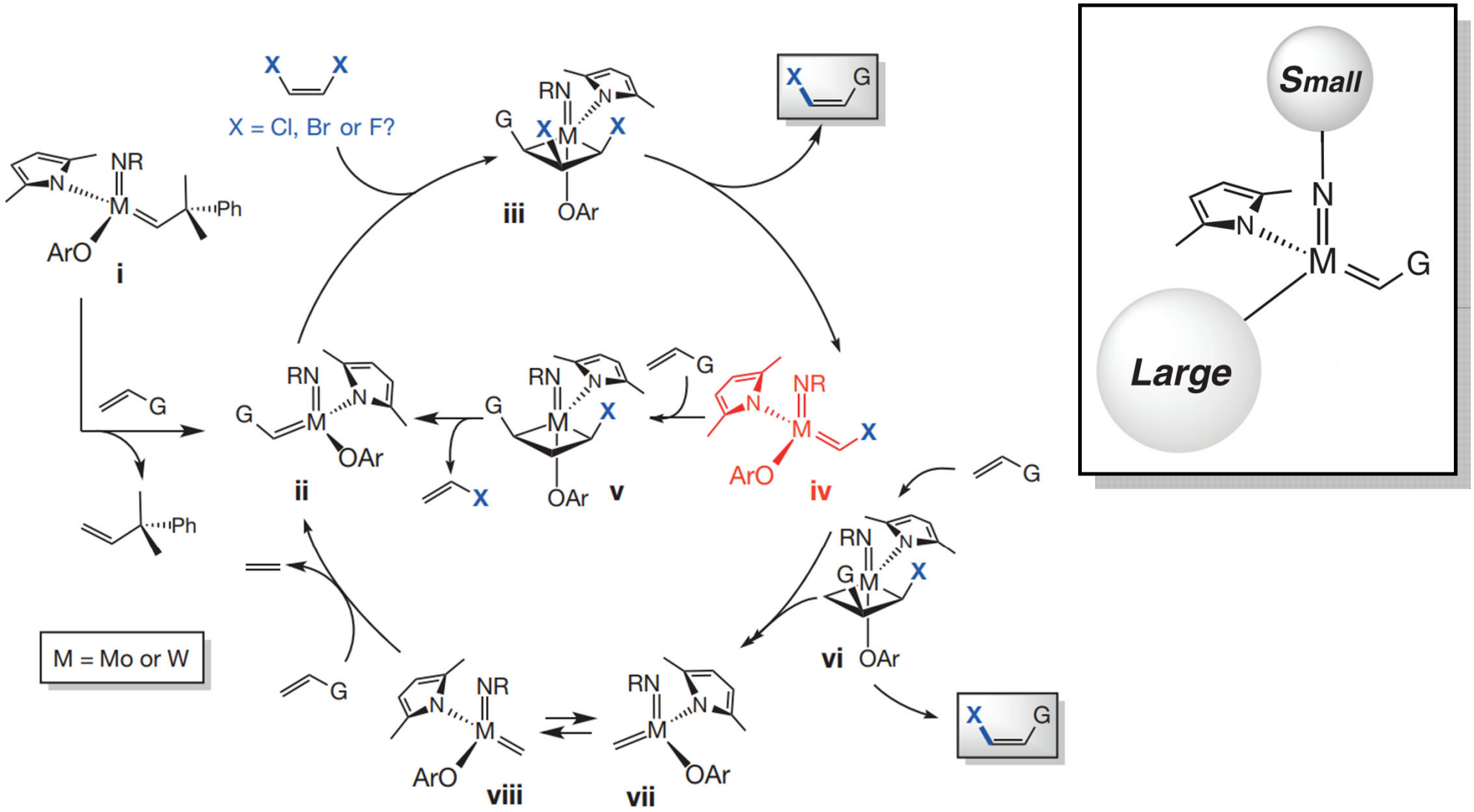
Grubbs: ~~Stability~~ or ~~Stereoselectivity~~





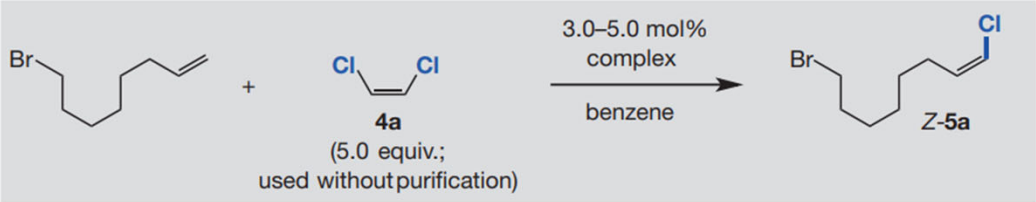
Hoveyda, A. et al. *Nature* **2016**, *531*, 459.

Schrock Cat.: Rational Design

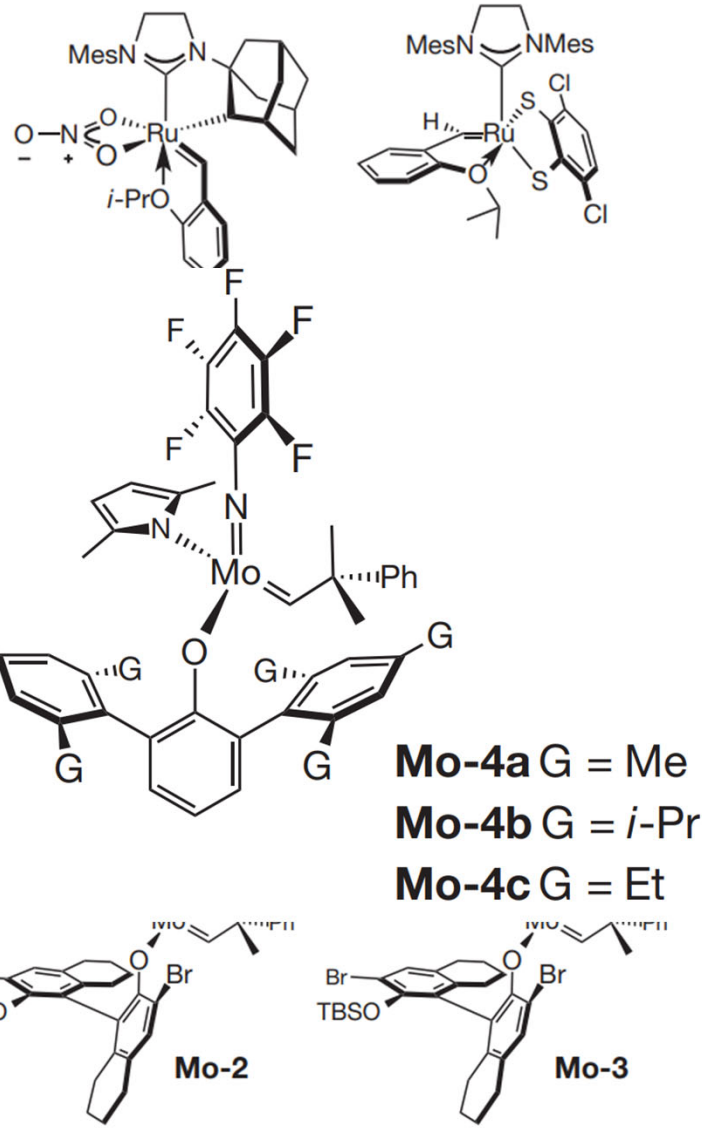


Hoveyda, A. et al. *Nature* **2016**, *531*, 459.

Steric & Reactivity & Stability

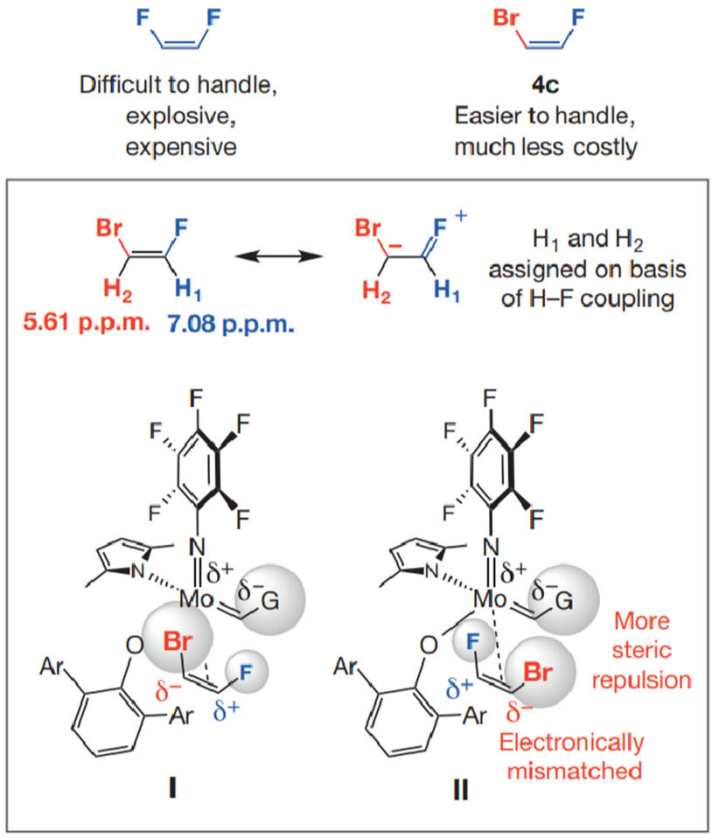


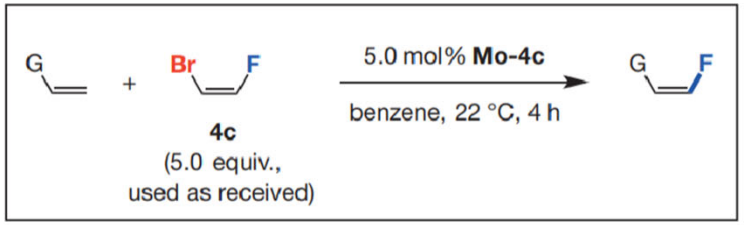
Entry number	Complex; loading (mol%)	Time (h); temperature (°C)	Conversion (%)*; yield (%)†	Z:E‡
1	**Ru-2**; 5.0	4; 50	82; 59	58:42
2	**Ru-3**; 5.0	4; 50	10; <5	NA
3	**Ru-4**; 5.0	4; 50	<10; <5	NA
4	**Mo-1**; 5.0	4; 22	67; <5	NA
5	**W-1**; 5.0	4; 22	45; <10	ND
6	**Mo-2**; 5.0	4; 22	43; <5	NA
7	**Mo-3**; 5.0	4; 22	60; 27	>98:2
8	**Mo-4a**; 5.0	4; 22	87; 60	>98:2
9	**Mo-4b**; 5.0	4; 22	62; 40	98:2
10	**Mo-4b**; 5.0	12; 22	95; 84	93:7
11	**Mo-4c**; 3.0	4; 22	90; 75	>98:2



Hoveyda, A. et al. *Nature* **2016**, *531*, 459.

Alkenyl Fluorides: Polarity Match





13a
>98% conv., 72:28 F:Br,
64% yield of fluoride,
>98:2 *Z*:*E*

13b
>98% conv., 96:4 F:Br,
70% yield of fluoride,
>98:2 *Z*:*E*

13c
>98% conv., 93:7 F:Br,
71% yield of fluoride,
95:5 *Z*:*E*

13d
84% conv., 96:4 F:Br,
72% yield of fluoride,
94:6 *Z*:*E*

13e
78% conv., 96:4 F:Br,
64% yield of fluoride,
97:3 *Z*:*E*

13f
88% conv., 95:5 F:Br,
66% yield of fluoride,
93:7 *Z*:*E*

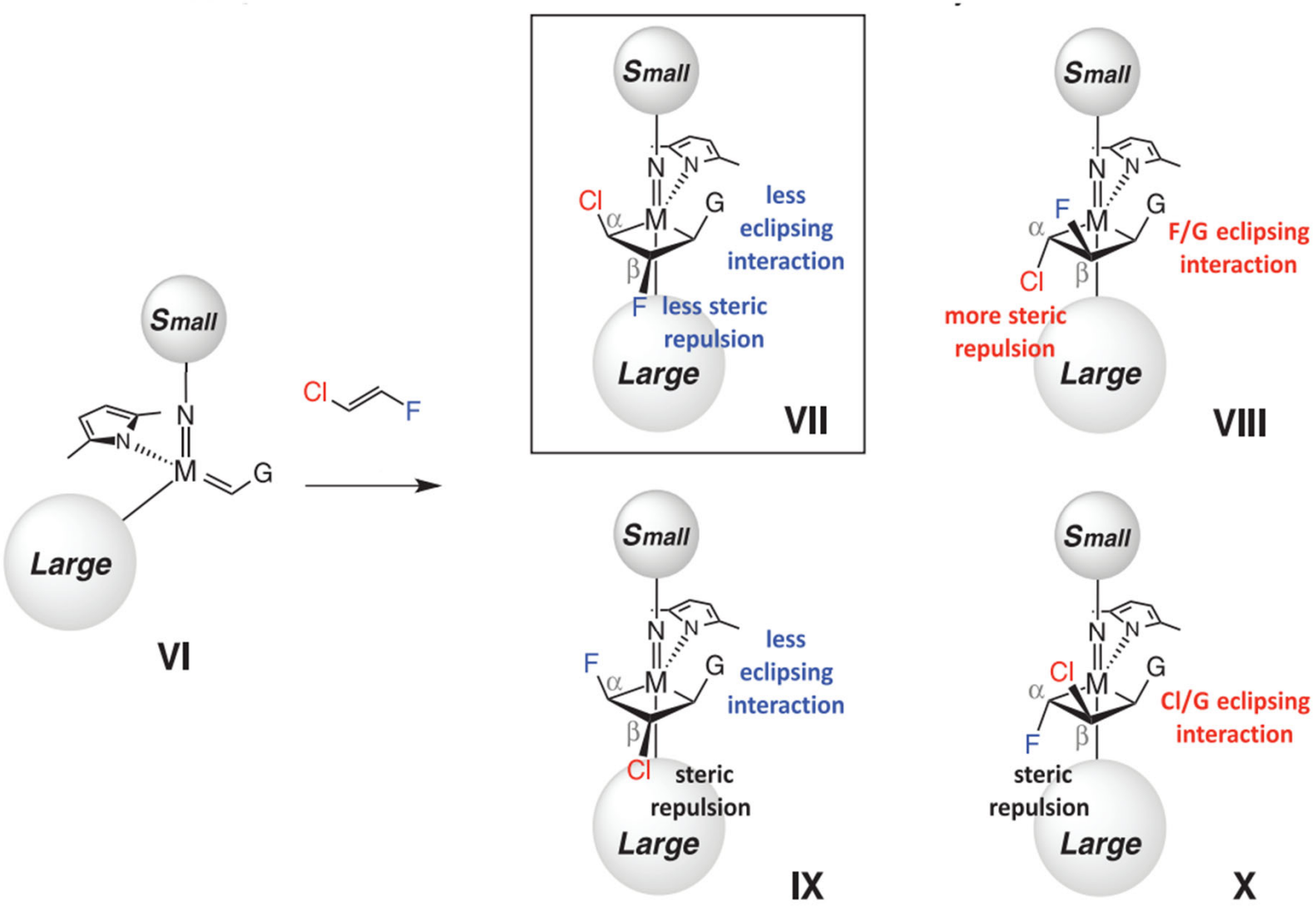
13g
(CM of TBS-amide/ deprotection)
60% conv., >98:2 F:Br,
55% overall yield of fluoride,
>98:2 *Z*:*E*

HCl
Ref. 7

14
GABA transaminase inhibitor
exhibits higher potency versus *E* isomer
and unique mode of action

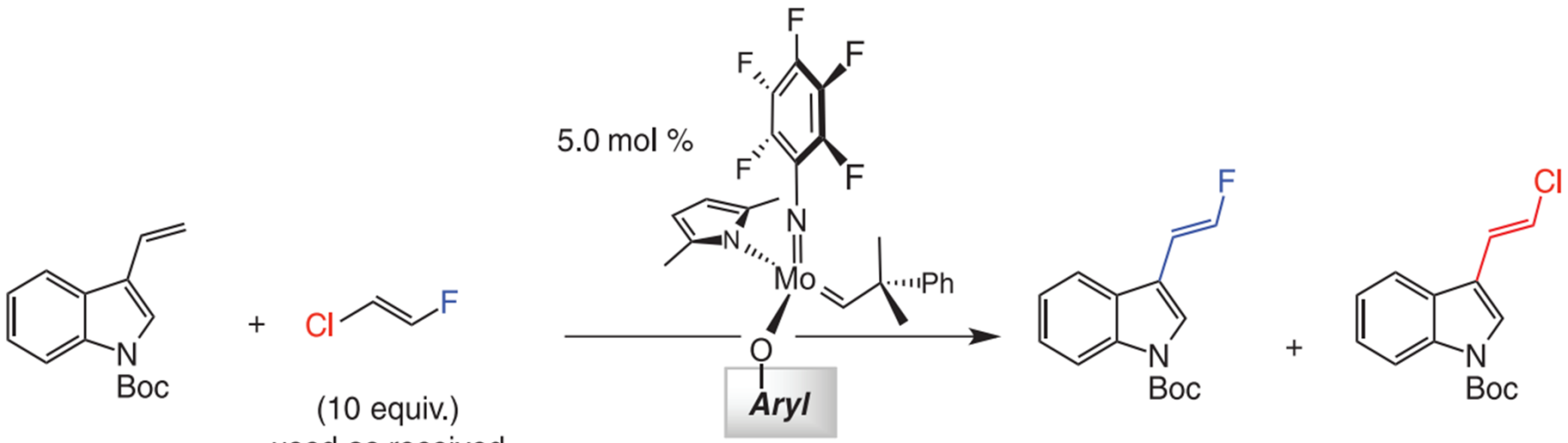
Hoveyda, A. et al. *Nature* **2016**, *531*, 459.

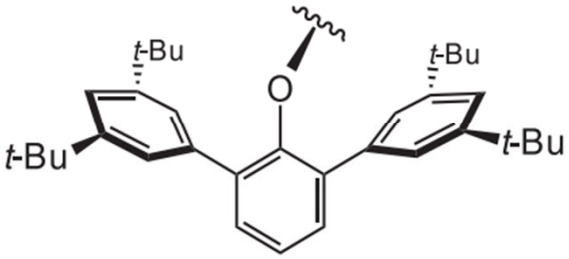
E-Selectivity: Gearing Effect



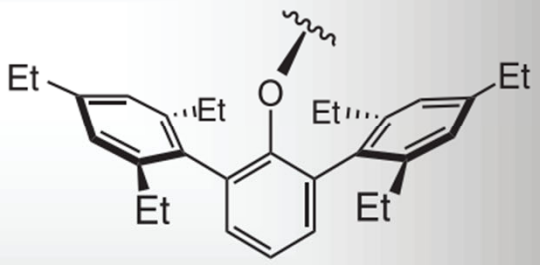
Hoveyda, A. et al. *Science* **2006**, *352*, 6285.

E-Selectivity: Gearing Effect





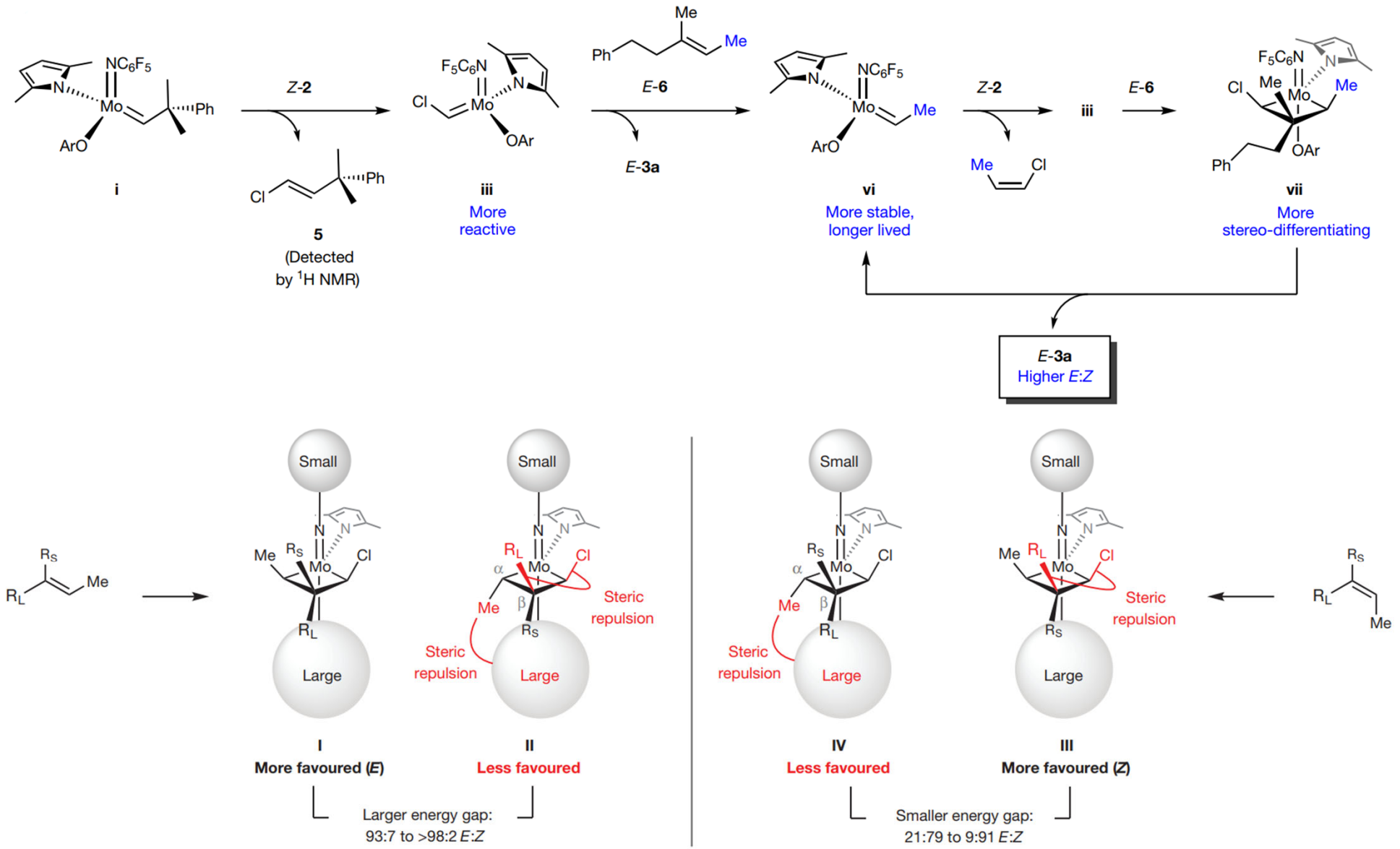
Mo-1d
>98% conv., **77:23 19a:4l**
>98:2 *E*:*Z* for either product



Mo-1a
>98% conv., **89:11 19a:4l**
>98:2 *E*:*Z* for either product
82% yield of pure fluoride

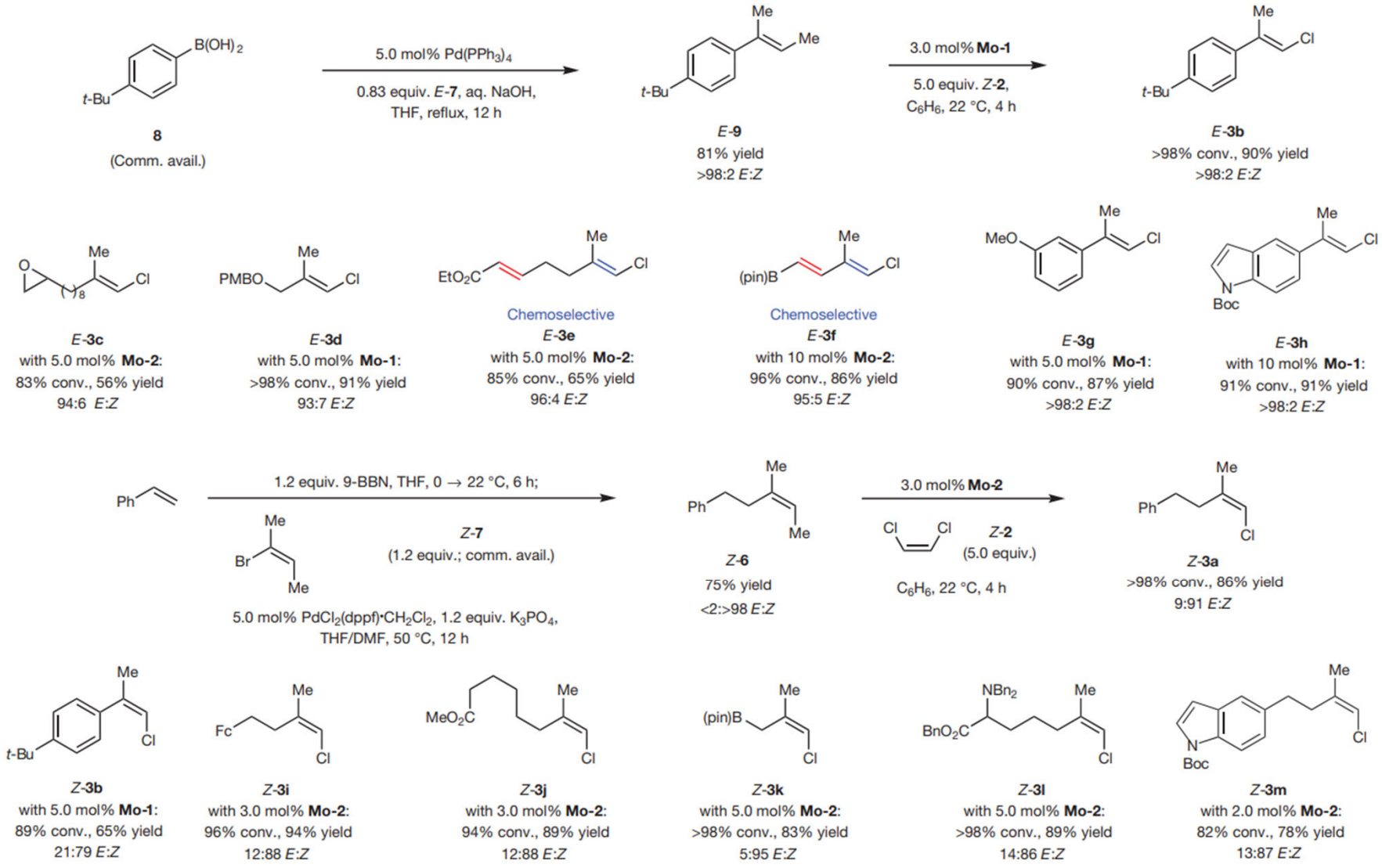
Hoveyda, A. et al. *Science* **2006**, *352*, 6285.

Z- & *E*-Configuration: Center-Control



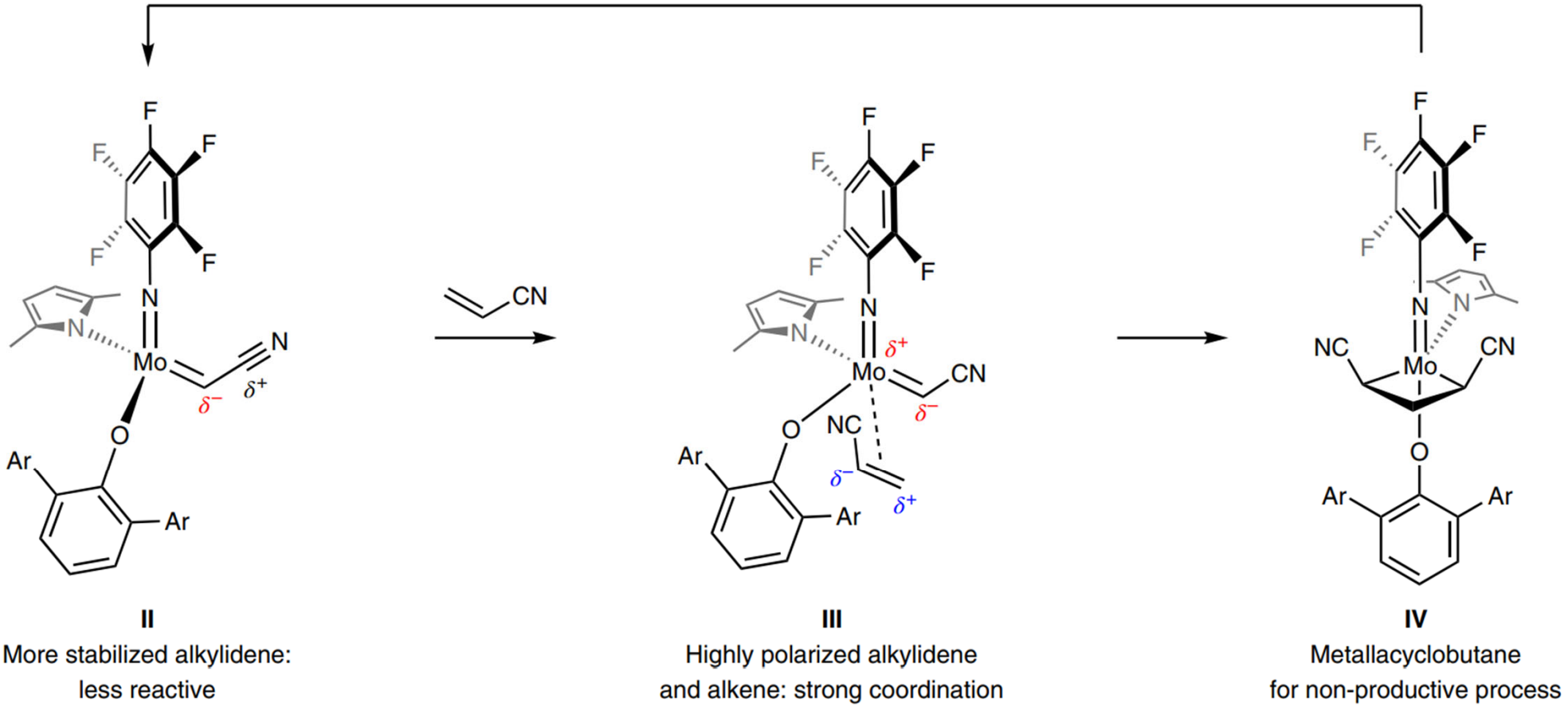
Hoveyda, A. et al. *Nature* **2017**, *552*, 347.

Z- & *E*-Trisubstituted Alkenyl Halides



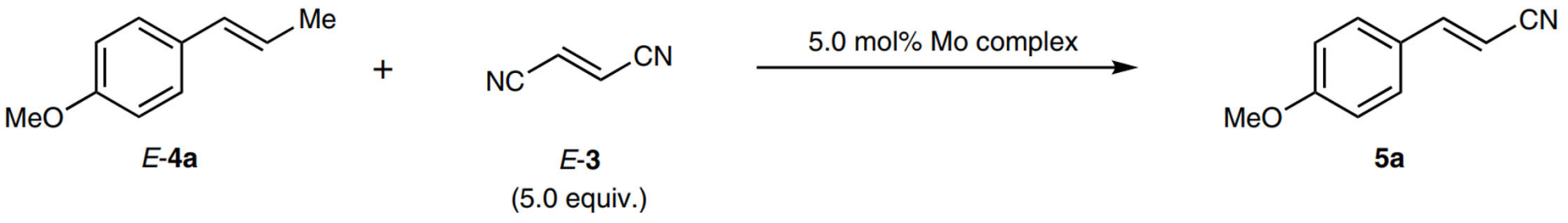
Hoveyda, A. et al. *Nature* **2017**, *552*, 347.

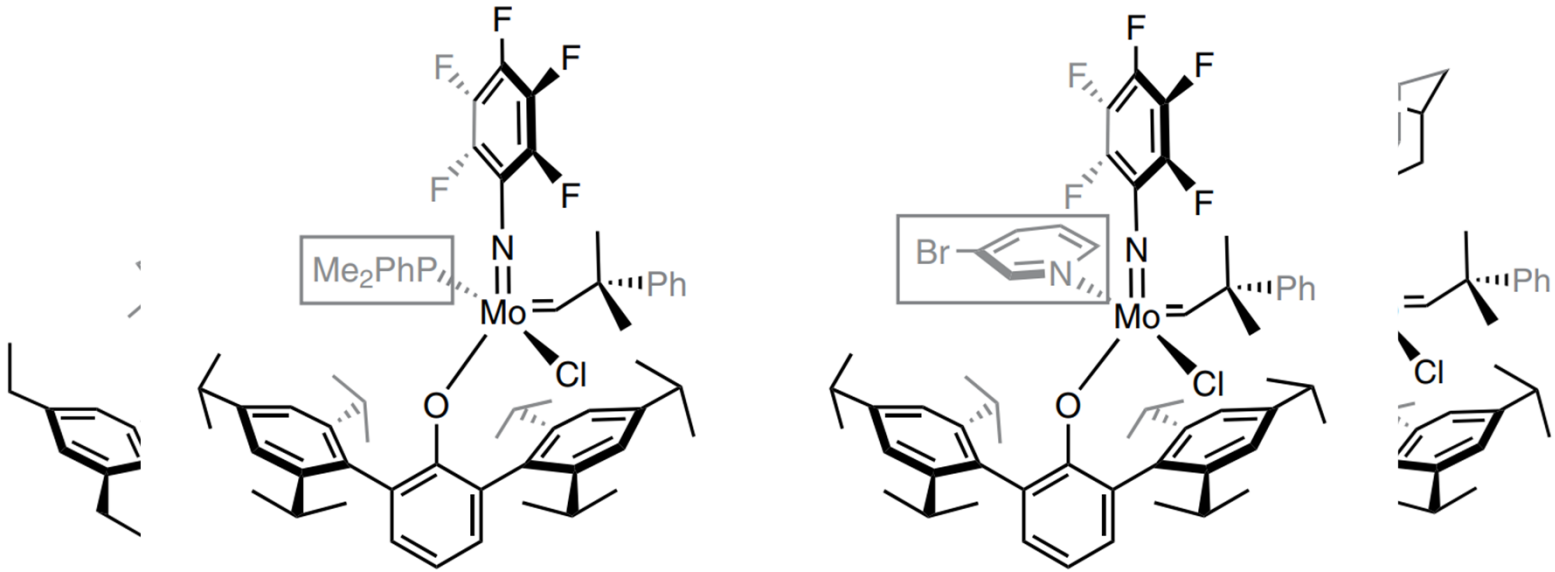
Alkenyl Nitriles: Forced Depolarization



Hoveyda, A. et al. *Nature Chemistry* **2019**, *11*, 478.

Alkenyl Nitriles: Forced Depolarization





Mo-2b

(C$_6$H$_6$, 15 mol% (C$_6$F$_5$)$_3$B, 40 °C, 12 h)
67% conv., 49% conv. to **5a**,
88:12 *E:Z*

Mo-2c

(C$_6$H$_6$, 6.0 mol% (C$_6$F$_5$)$_3$B, 40 °C, 12 h)
>98% conv., 84% conv. to **5a**,
78% yield, 96:4 *E:Z*

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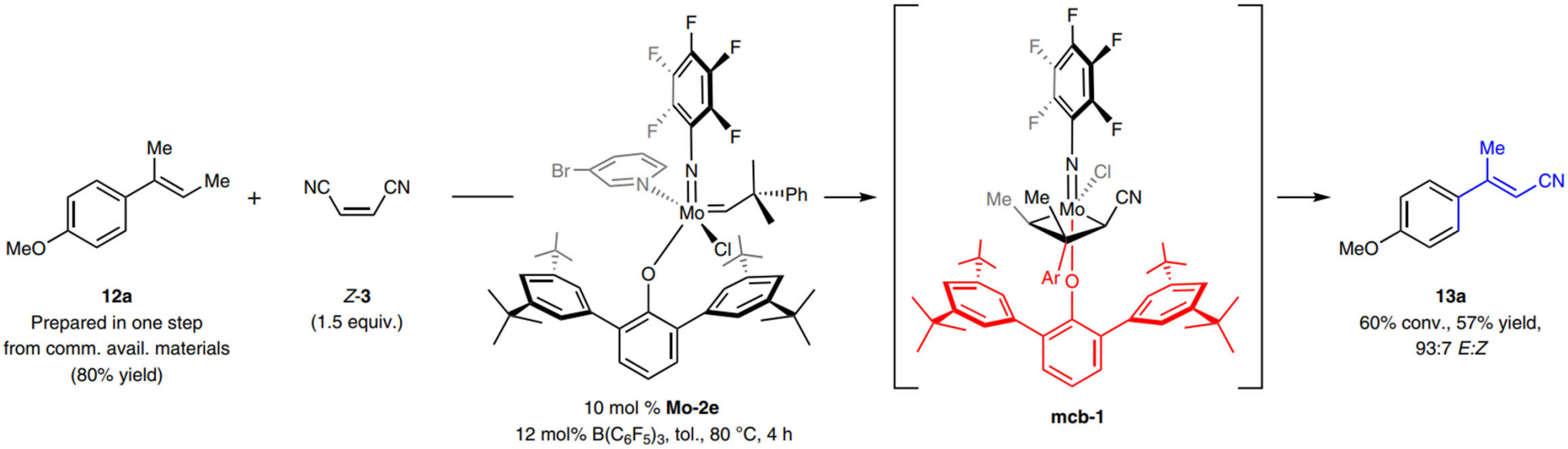
Alkenyl Nitriles: Forced Depolarization



Hoveyda, A. et al. *Nature Chemistry* **2019**, *11*, 478.

Outline

- **Introduction**
- **Classical Catalysts System**
  Schrock Catalysts
  Grubbs Catalysts
  RCM Reaction
  Classical CM Reaction
- **Catalysts Improvement**
  Restrictions of Classical Catalysts
  Solutions of Grubbs Catalysts
  Solutions of Schrock Catalysts
- **Summary**
- **Acknowledgement**

Summary

- Normal-Schrock Carbene: Suitable
- Schrock: Ring Formation Determining
- Grubbs: Coordination vs. Ring Formation
- Nucleophilic Mo Carbene & Electrophilic Ru Carbene
- Electronic Effect of Olefins: Fast ≠ Suitable
- Complex to Ring: Electron-Withdrawing Preference
- Grubbs System Improvement: Attacking Direction
- Schrock System Improvement: Stereo-Differentiating
- Carbene with Functional Groups: Back to Suitable Carbene
- A Story of Catalyst Development: To be Continued…