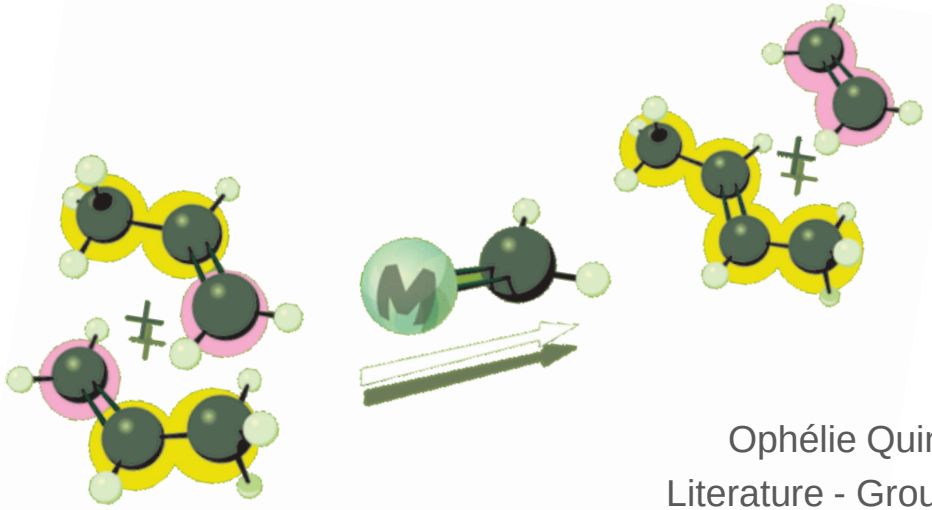
New perspectives in metal-catalyzed metathesis:

Alkyne and Z-selective olefin metathesis,
new powerful tools for total synthesis



Ophélie Quinonero

Literature - Group Meeting

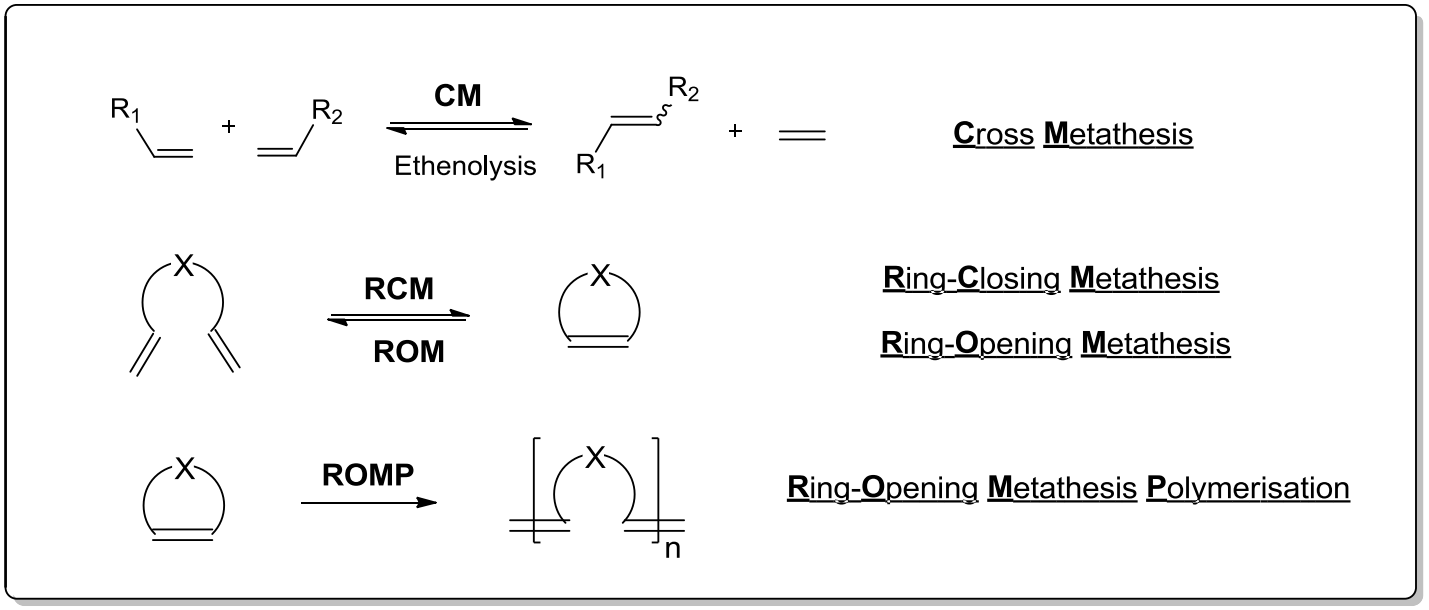
31/03/2014

Introduction

Metathesis: a change-your-partner dance

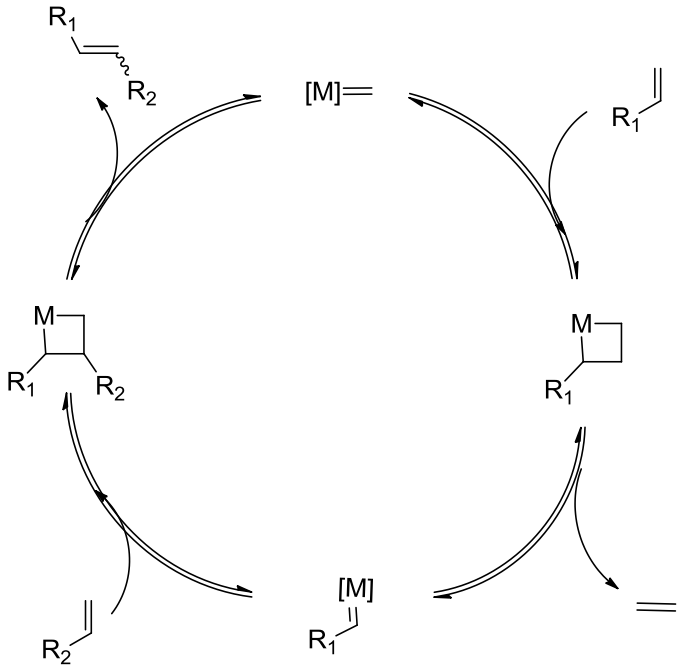
- From the greek (μετάθεσις) means « **transposition** »

- Powerful C=C bond forming reaction



Introduction

The Chauvin Mechanism



- Thermodynamic control

- Reversibility of all the steps

J.-L. Hérisson and Y. Chauvin, *Makromol. Chem.*, **1971**, 141, 161

Overview

I- Introduction

- The early days
- Non-selective catalysts

II- Z-selectivity

- Z-selective methodologies : The early steps

- Z-selective strategies
- Alkyne metathesis/Z-selective hydrogenation
  - Alkyne metathesis / Introduction
  - Alkyne metathesis / Catalysts
- Silicon Tethering
- Indirect substrate Control: Removable silyl groups
- Templated RCM

- Z-selective catalysts
- Molybdnemun- and Tungsten-Based catalysts
- Ruthenium catalysts

III - Selected Total Synthesis Applications

- Concise total synthesis of epothilone A and C
- Total synthesis of Nakadomarin A
- Concise total synthesis of epothilone D
- Key step en route to oximidine III

Conclusion

I - Introduction

Olefin metathesis : the early days

1931

First observation of the metathesis :
Propene gives ethylene and 2-butene at **725 °C**

From a review : D. Astruc, *New. J. Chem*. **2005**, 29, 42-56

I - Introduction

Olefin metathesis : the early days

1931

1950's

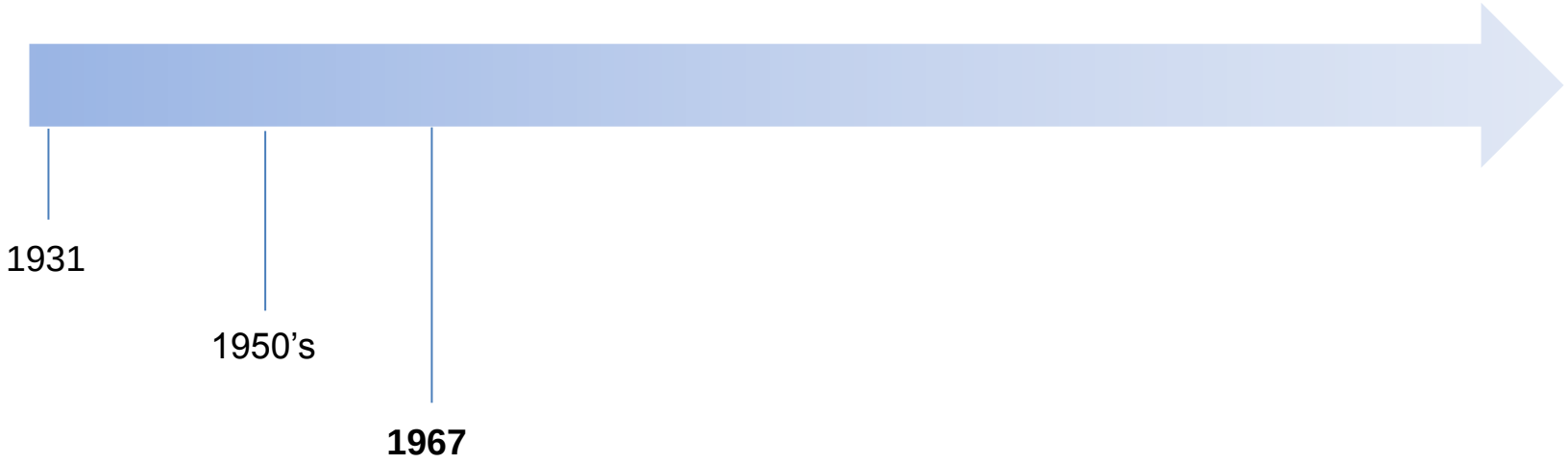
First catalyzed metathesis reaction :

Propene gives ethylene and 2-butene by heating with **Molybdenum** on Alumina

(by Du Pont, Standard Oil an Phillips Petroleum)

I - Introduction

Olefin metathesis : the early days



The name « metathesis » was given for the first time by Calderon

Calderon, *Tetrahedron Lett*. **1967**, 34, 33-27

I - Introduction

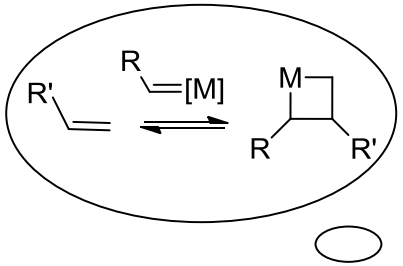
Olefin metathesis : the early days

1931

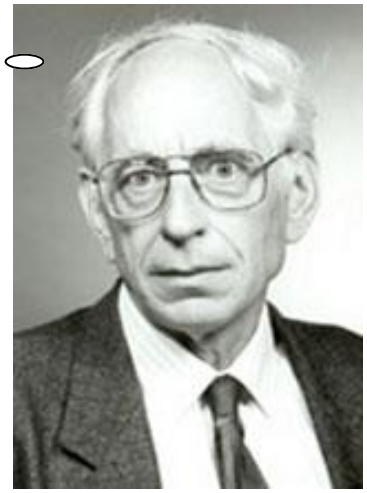
1950's

1967

1971



The Chauvin mechanism



I - Introduction

Olefin metathesis : the early days

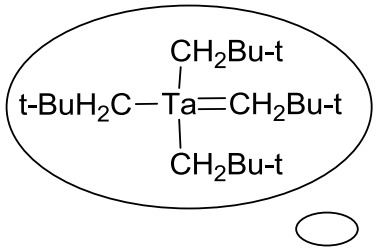
1931

1950's

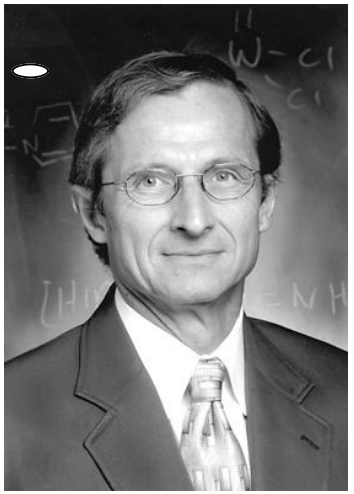
1967

1971

1974



First isolated metal-alkylidene complex by Schrock



R. R. Schrock, *J. Am. Chem. Soc.,* **1974**, 96, 6796
R. R. Schrock,, *J. Am. Chem. Soc.,* **1975**, 97, 6577

I - Introduction

Olefin metathesis : the early days

1931

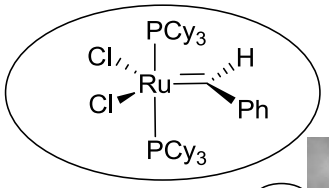
1950's

1967

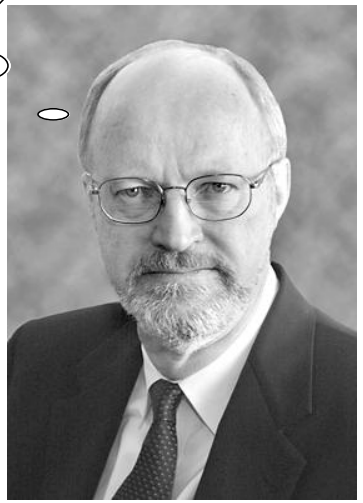
1971

1974

1992



First isolated Ru=carbene metathesis catalyst complex by Grubbs



I - Introduction

Olefin metathesis : the early days

1931

1950's

1967

1971

1974

1992

2005

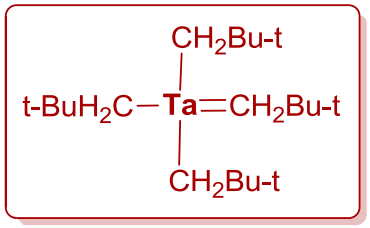
Nobel Prize

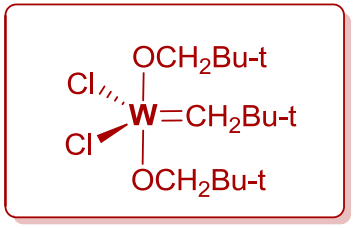
To Yves Chauvin, Robert H. Grubbs and Richard R. Schrock

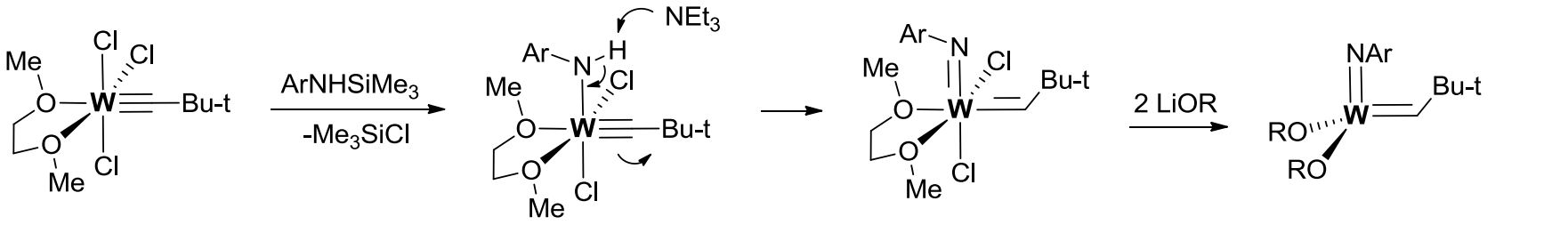
"for the development of the metathesis method in organic synthesis"

I - Non-selective catalysts

Early Tantalum and Tungsten complexes







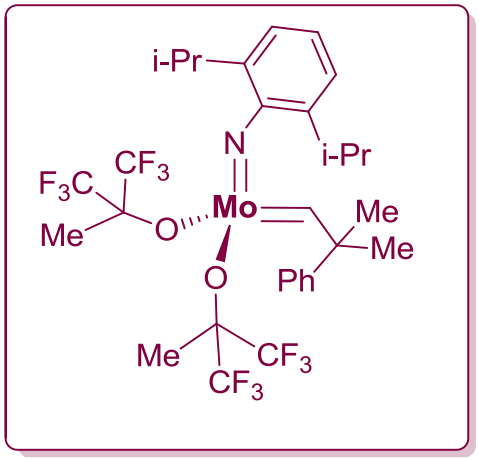
Ar = 2,6-i-$Pr_2C_6H_3$
R= t-Bu, $C(CH_3)(CF_3)_2$,
$C(CH_3)_2(CF_3)$, 2,6-i-$Pr_2C_6H_3$

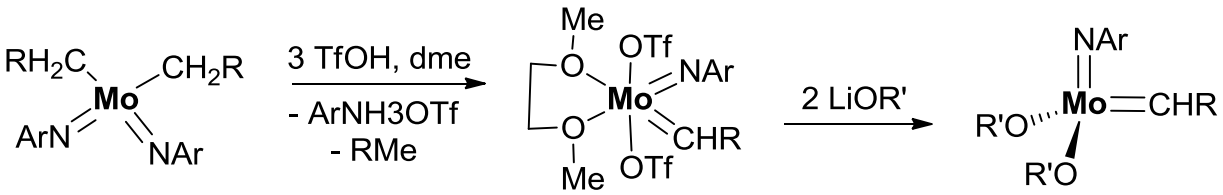
J. Kress, M. Wesolek and J. A. Osborn,*Chem. Commun.,***1982**, 514.

I - Non-selective catalysts

Molybdenum complexes

Schrock catalyst :

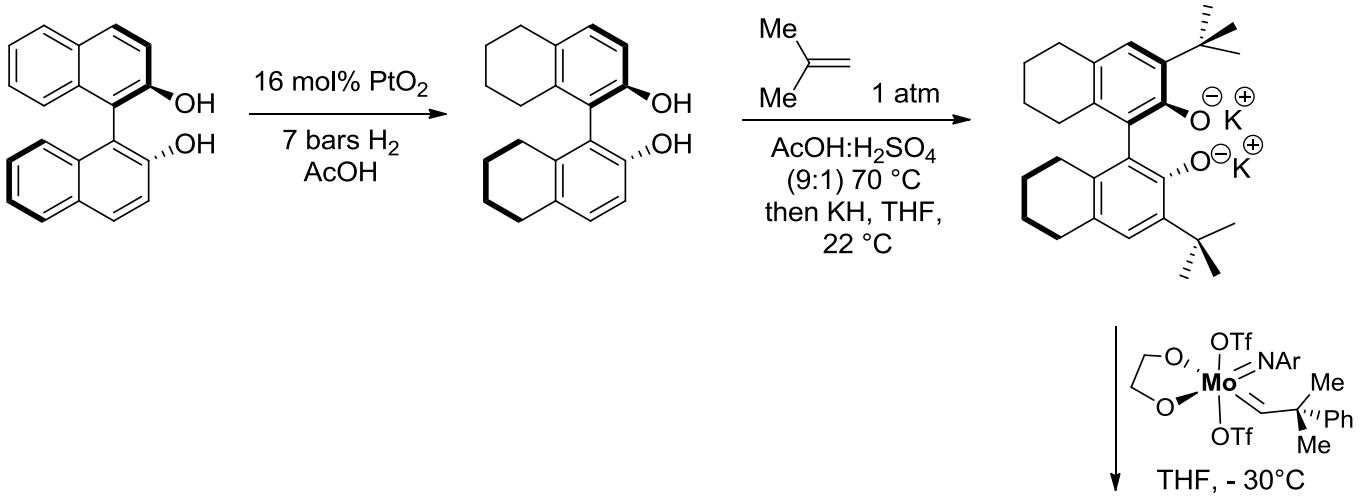




J. S. Murdzek and R. R. Schrock, *Organometallics*, **1987**, 6, 1373
R. R. Schrock, et al, *J. Mol. Catal*., **1988**, 46, 243

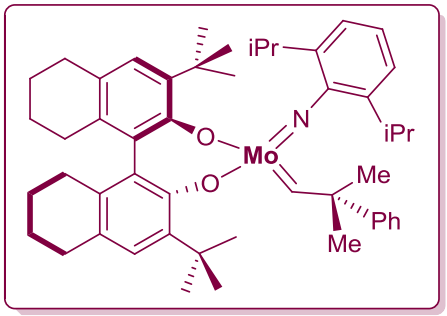
I - Non-selective catalysts

Molybdenum complexes



Mo-based chiral metathesis catalyst :

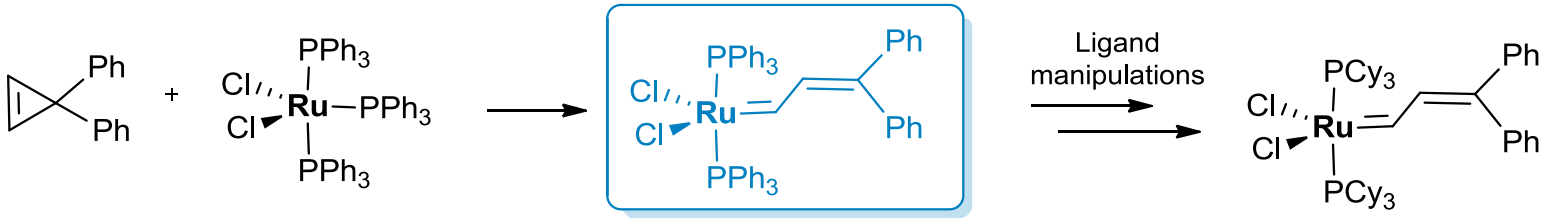
Easier preparation



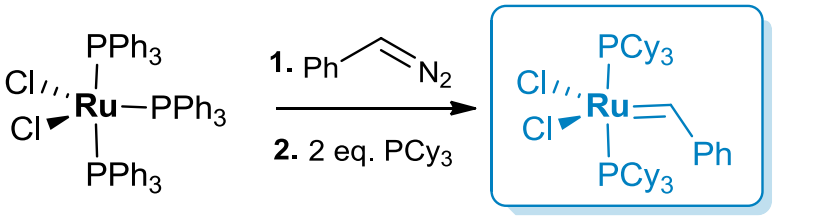
S. L. Aeilts, D. R. Cefalo, P. J. Bonitatebus, Jr., J. H. Houser, A. H. Hoveyda and R. R. Schrock, *Angew. Chem., Int. Ed.*, **2001**, 40,1452.

I - Non-selective catalysts

Ruthenium complexes



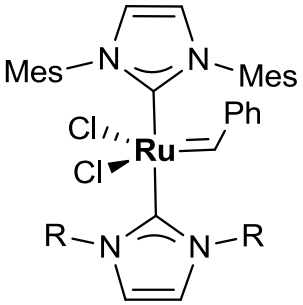
First metathesis-active ruthenium carbene

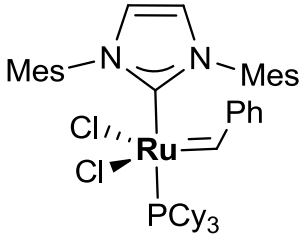


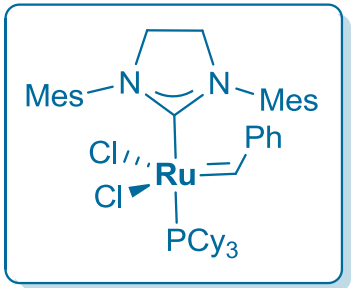
"First generation" catalyst (Grubbs I)

S. T. Nguyen, L. K. Johnson, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, **1992**,114, 3974
P. Schwab, M. B. France, J. W. Ziller and R. H. Grubbs, *Angew. Chem. Int. Ed.*, **1995**,34, 2039

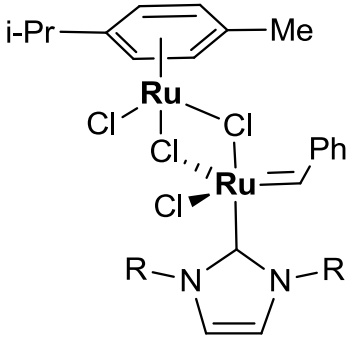
I - Non-selective catalysts
Ruthenium complexes

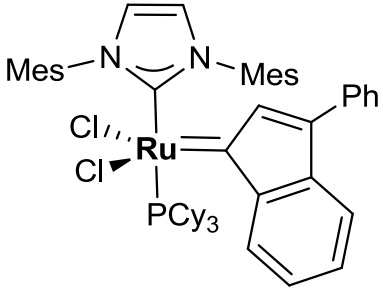






"Second-generation" Grubbs catalyst (Grubbs II)

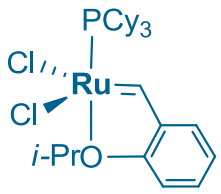




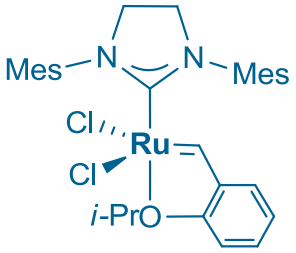
W. A. Herrmann *et al*, *Angew. Chem. Int. Ed.,* **1998**, 37, 2490
R. H. Grubbs *et al, Tetrahedron Lett.,* **1999**, 40, 2247
S. P. Nolan *et al, J. Am.Chem. Soc.,* **1999**,121, 2674

I - Non-selective catalysts

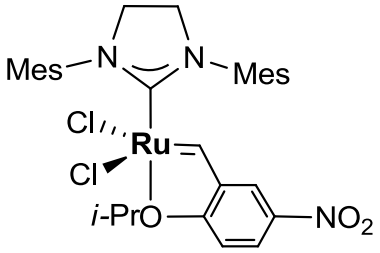
Carbene modifications

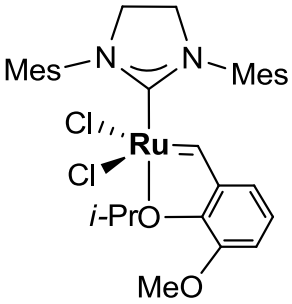


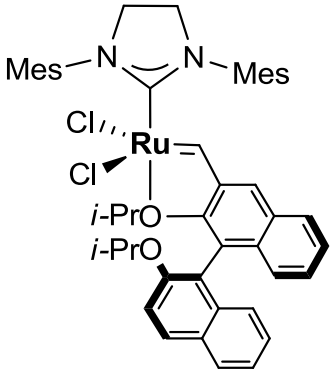
Hoveyda-Grubbs Catalyst
1st Generation

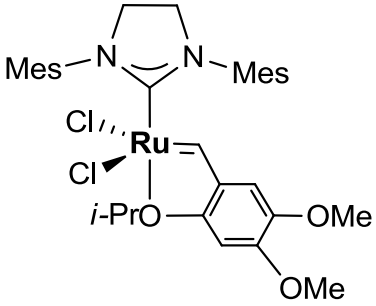


Hoveyda-Grubbs Catalyst
2nd Generation









A. H. Hoveyda *et al*, *J. Am.Chem. Soc.,* **2000**,122, 8168
S. Blechert *et al*,*Tetrahedron Lett.,* **2000**,41, 9973

Overview

I- Introduction

- The early days
- Non-selective catalysts

II- Z-selectivity

- **Z-selective methodologies : The early steps**
- **Z-selective strategies**
  - Alkyne metathesis/Z-selective hydrogenation
    - Alkyne metathesis / Introduction
    - Alkyne metathesis / Catalysts
  - Silicon Tethering
  - Indirect substrate Control: Removable silyl groups
  - Templated RCM
- **Z-selective catalysts**
  - Molybdnemun- and Tungsten-Based catalysts
  - Ruthenium catalysts

III - Selected Total Synthesis Applications

- Concise total synthesis of epothilone A and C
- Total synthesis of Nakadomarin A
- Concise total synthesis of epothilone D
- Key step en route to oximidine III

Conclusion

II – Z-selectivity

- **Challenge: control the geometry of the forming double bond**

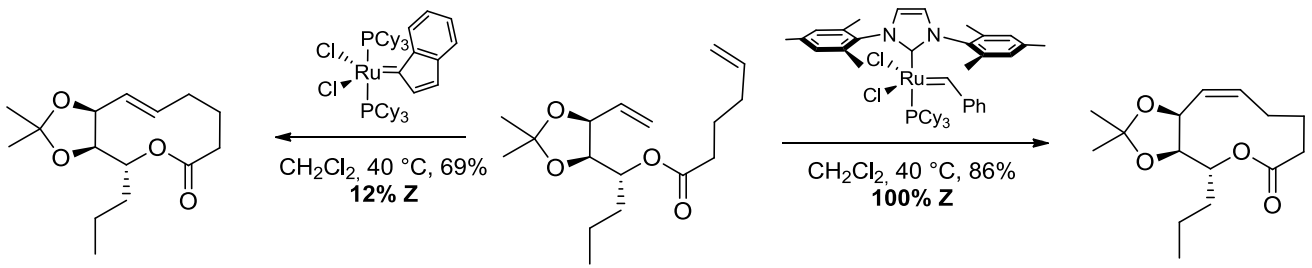
⟶ Except for small cycles, **mixture of Z/E product**

⟶ Reversibility of the reaction : olefin products can isomerize.

⟶ First example of Z-selectivity by Schrock and Hoveyda in 2009

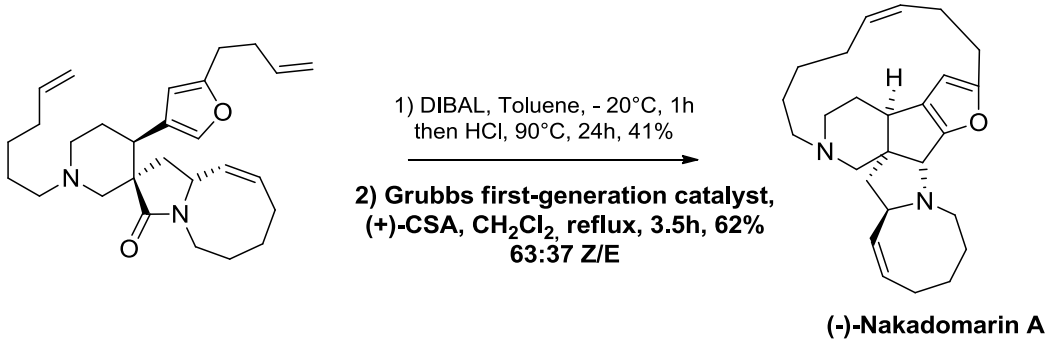
II - Z-selective methodologies : The early steps
Experimental observations / Substrate control

- Thermodynamic vs kinetic effect



A. Fürstner *et al J. Am. Chem. Soc.* **2002**, 124, 7061-7069

- Amine protonation



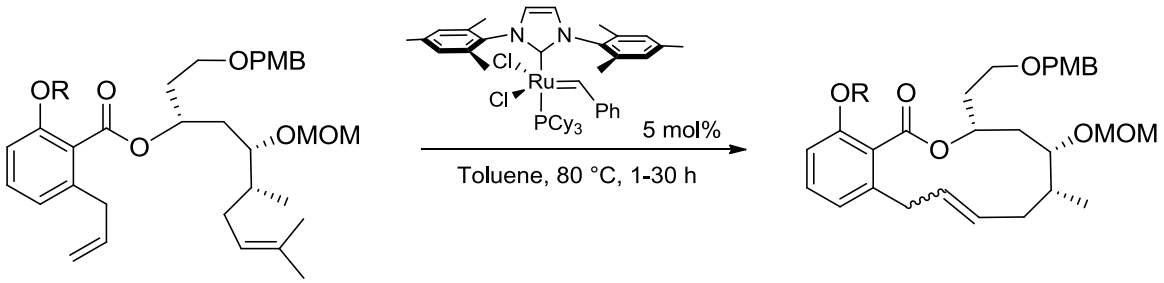
First example where an **E/Z selectivity was reversed** when protonated amines were used

P. Jakubec, D. M. Cockfield, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, 131,16632

II - Z-selective methodologies : The early steps

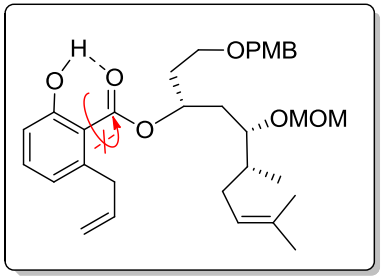
Experimental observations / Substrate control

- Remote substituent effects



R	Yield (%)	E:Z
H	**69**	**0:100**
TBS	91	40:60
MOM	91	68:32
Me	93	66:34

→ **Unexpected (Z)-configuration**

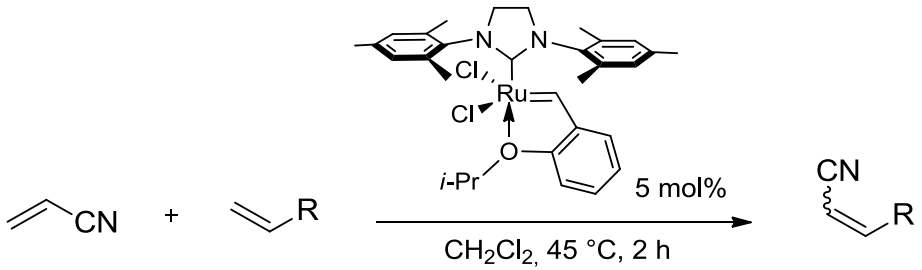


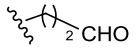
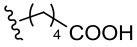
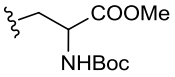
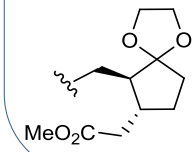
A. Fürstner, O. R. Thiel, G. Blanda, *Org. Lett*. **2000**, 2, 3731.

II - Z-selective methodologies : The early steps

Experimental observations / Substrate control

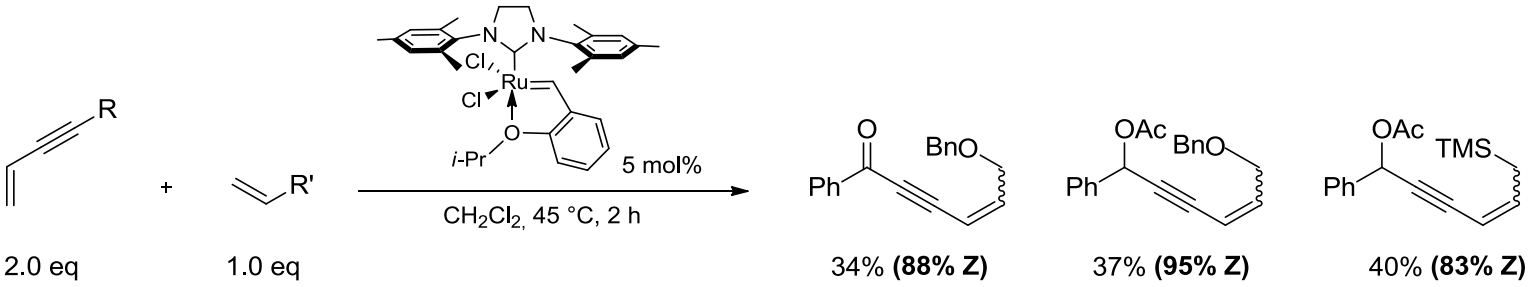
- Acrylonitrile



R	Yield (%)	E:Z
	91	20:80
	76	25:75
	91	20:80
	83	10:90

Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett*. **2001**, 3, 430-432

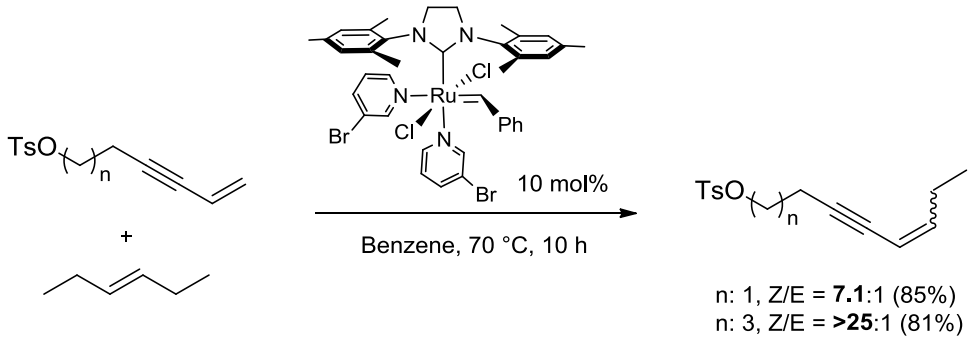
- Enyne

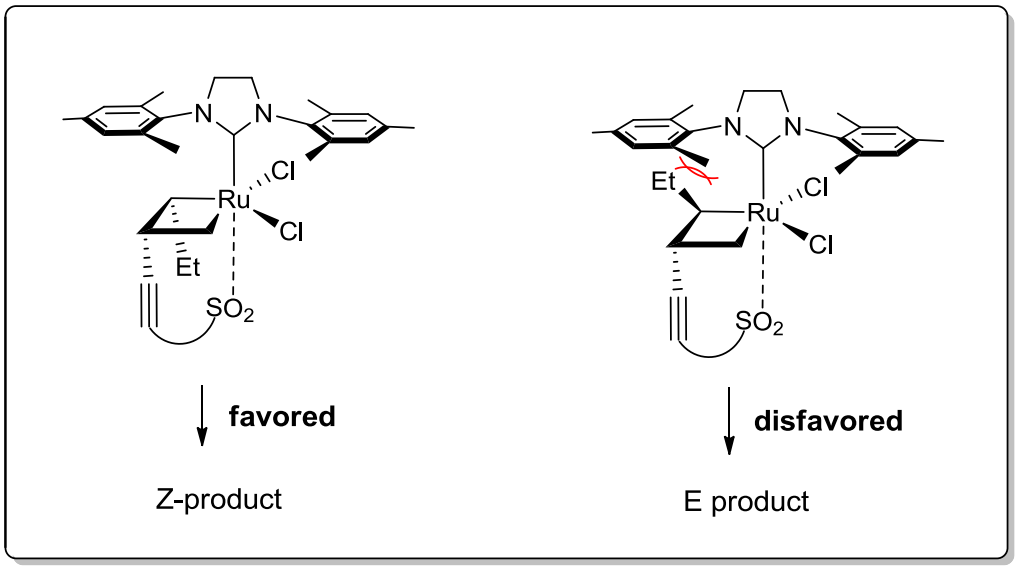


Hansen, E. C.; Lee, D. *Org. Lett.* **2004**, 6, 2035-2038

II - Z-selective methodologies : The early steps

Experimental observations

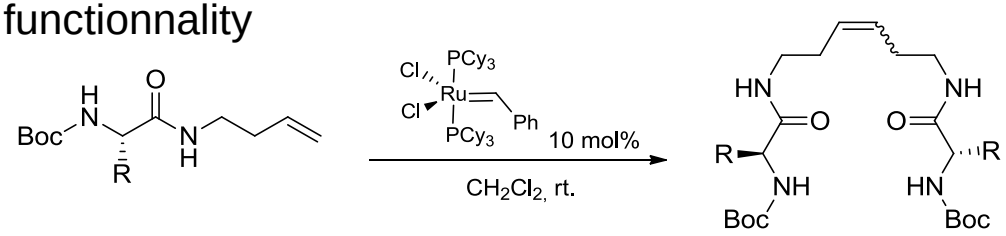


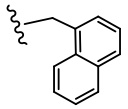
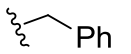
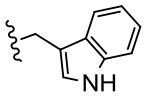
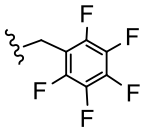
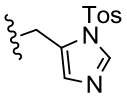
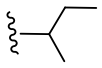


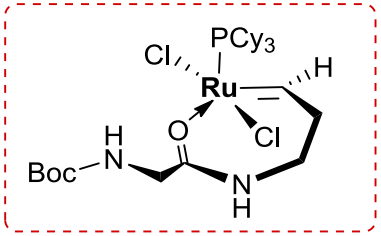
B. Kang, J. M. Lee, J. Kwak, Y. S. Lee, S. Chang, *J. Org. Chem.* **2004**, 69,7661.

II - Z-selective methodologies : The early steps
Experimental observations / Substrate control

- Effect of remote functionnality



R	Yield (%)	Z:E	R	Yield (%)	Z:E
H	0			91	1.6:1
	77	3:1			
	89	3:1		0	
	0			0	
	0				

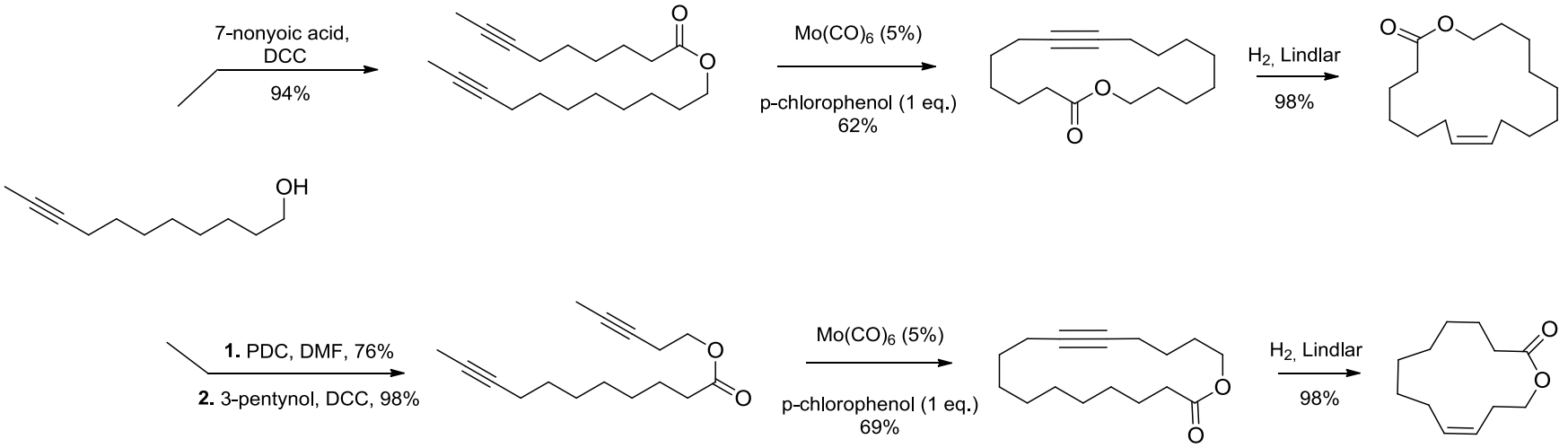


Potential non-productive chelate of ruthenium carbene

B. R. McNaughton, K. M. Bucholtz, A. Camaaño-Moure, B. L. Miller, *Org.Lett.* **2005**, 7, 733.

II - Z-selective strategies

Alkyne metathesis/Z-selective hydrogenation



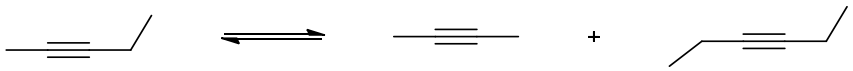
A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, 121,11108.

II - Z-selective strategies: Alkynes metathesis/Z-selective hydrogenation

Alkynes metathesis: Introduction

-**1968**, Penella *et al « Disproportion of Alkynes »*

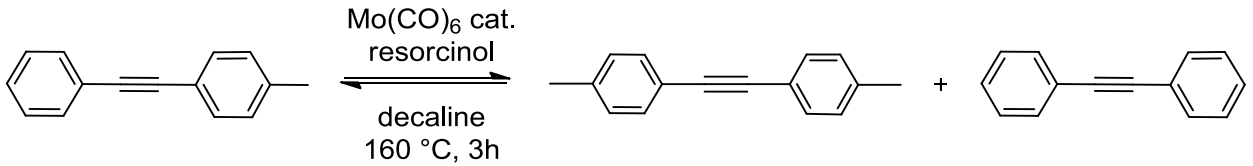
→ Using heterogeneous mixture of **tungsten oxides and silica**
→ High temperature (**200-450 °C**)



F. Pennella, R. L. Banks and G. C. Bailey, *Chem.Commun*., **1968**, 1548.

- **1974**, Mortreux

→ Using homogeneous mixture of **$Mo(CO)_6$** and simple **phenol additives** in high boiling solvents

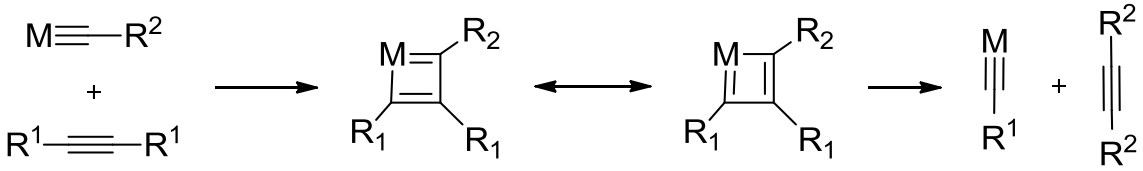


A. Mortreux and M. Blanchard, *Chem. Commun*., **1974**,786.

II - Z-selective strategies: Alkynes metathesis/Z-selective hydrogenation

Alkynes metathesis: Introduction

-**1975**, Katz *et al* **proposed** that **metal carbynes** likely account for the catalytic turnover in a sequence [2+2] cycloaddition and cycloreversion



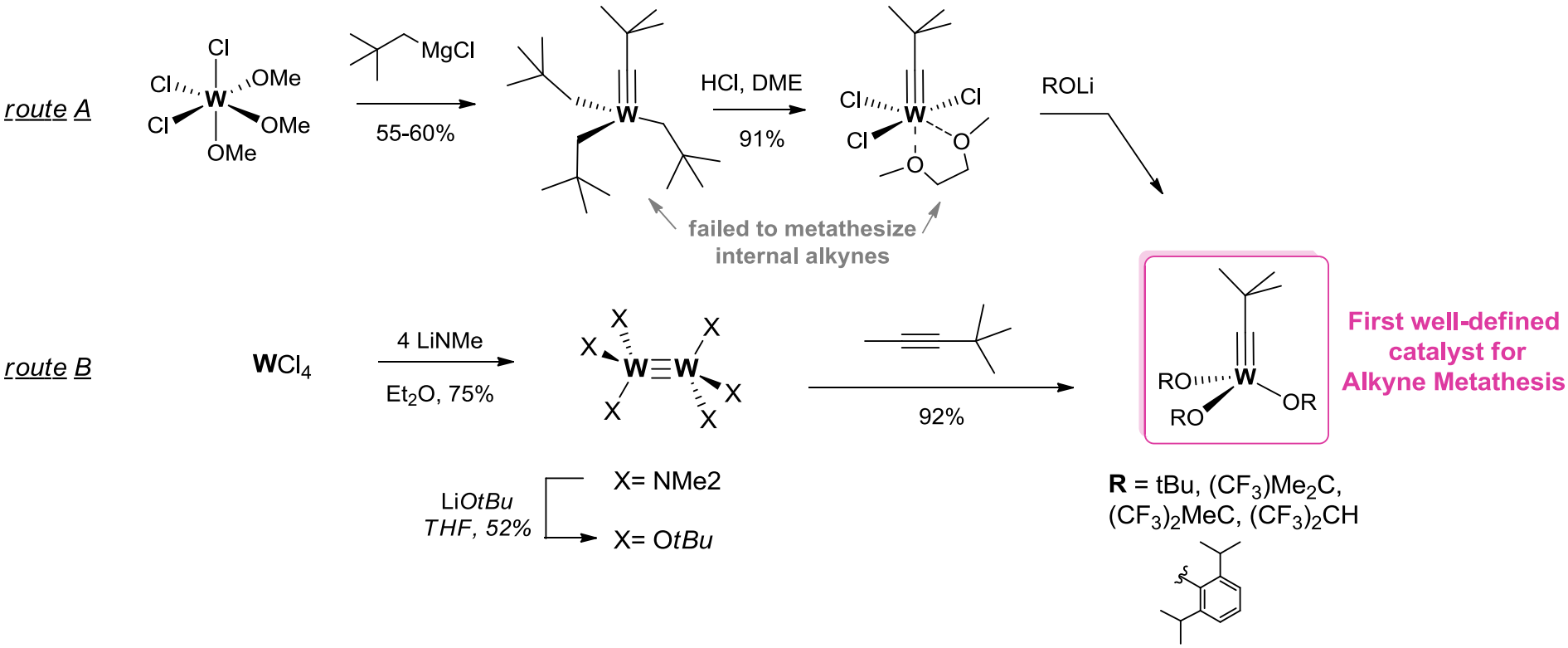
T. J. Katz and J. McGinnis, *J. Am. Chem. Soc.,* **1975**, 97,1592

- **1981**, Schrock experimentally **established this mechanism** using high valent metal alkylidines

J. H. Wengrovius, J. Sancho and R. R. Schrock, *J. Am. Chem.Soc*., **1981**, 103, 3932

II - Z-selective strategies: Alkynes metathesis/Z-selective hydrogenation

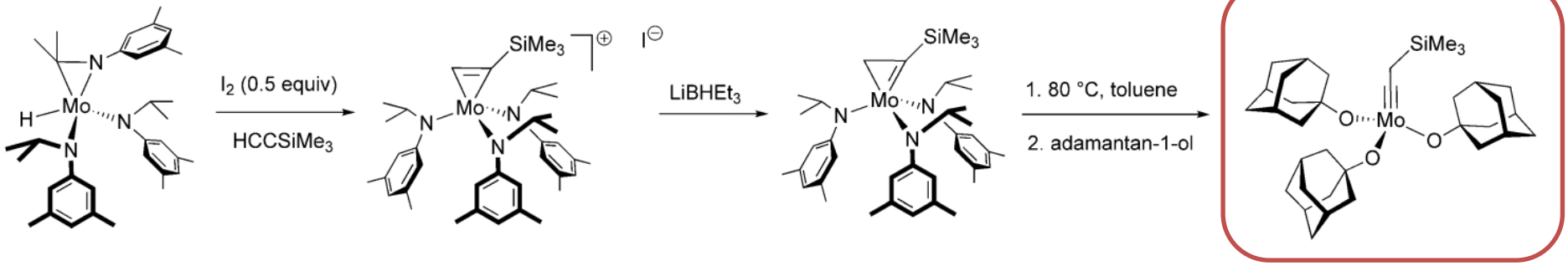
Alkynes metathesis: Tungsten catalysts



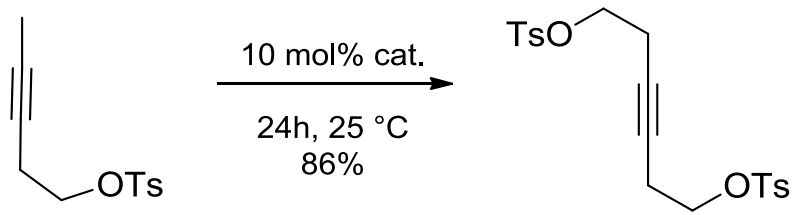
J. H. Wengrovius, J. Sancho, R. R. Schrock, *J. Am. Chem.Soc.* **1981**, 103, 3932 – 3934

II - Z-selective strategies: Alkynes metathesis/Z-selective hydrogenation

Alkynes metathesis: Molybdenum-based catalysts



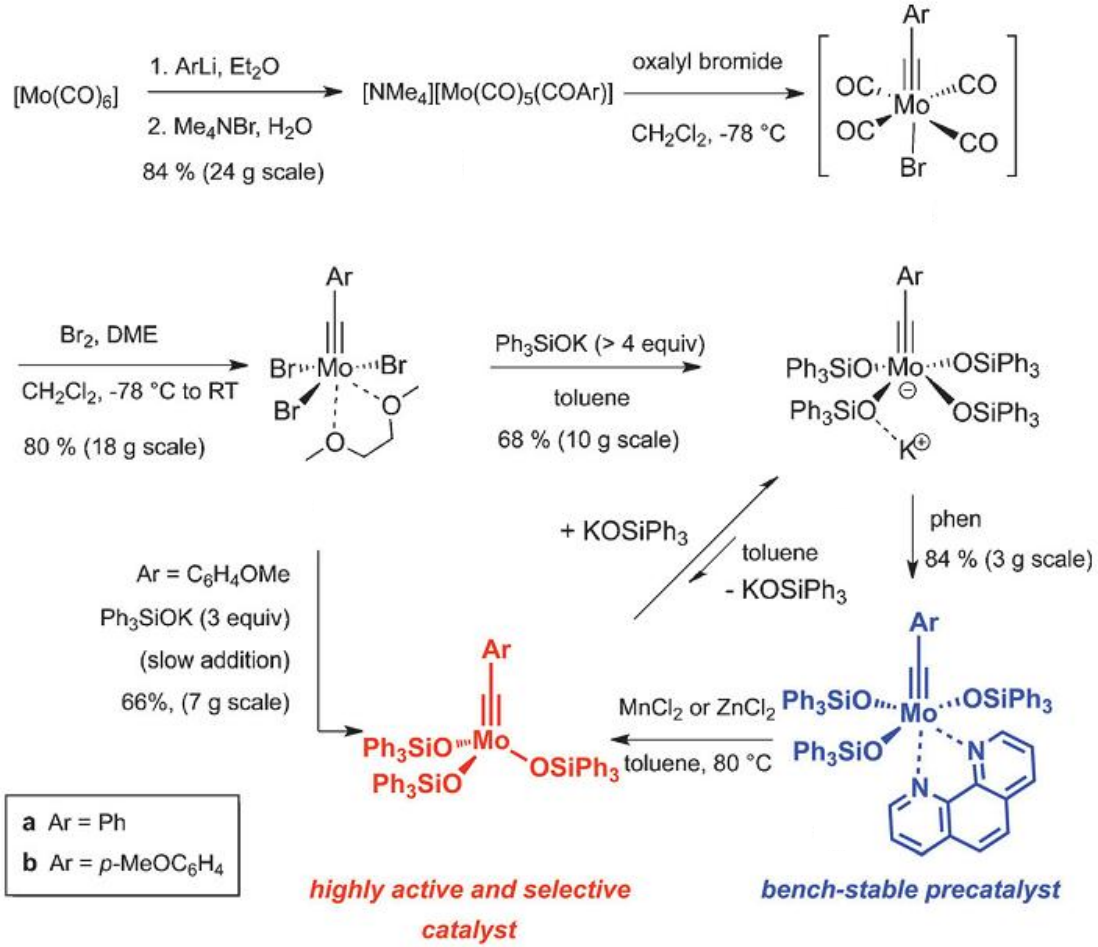
metathesis-active molybdenum alkylidyne



Y.-C. Tsai, P. L. Diaconescu, C. C. Cummins, *Organometallics,* **2000**, 19, 5260 – 5262

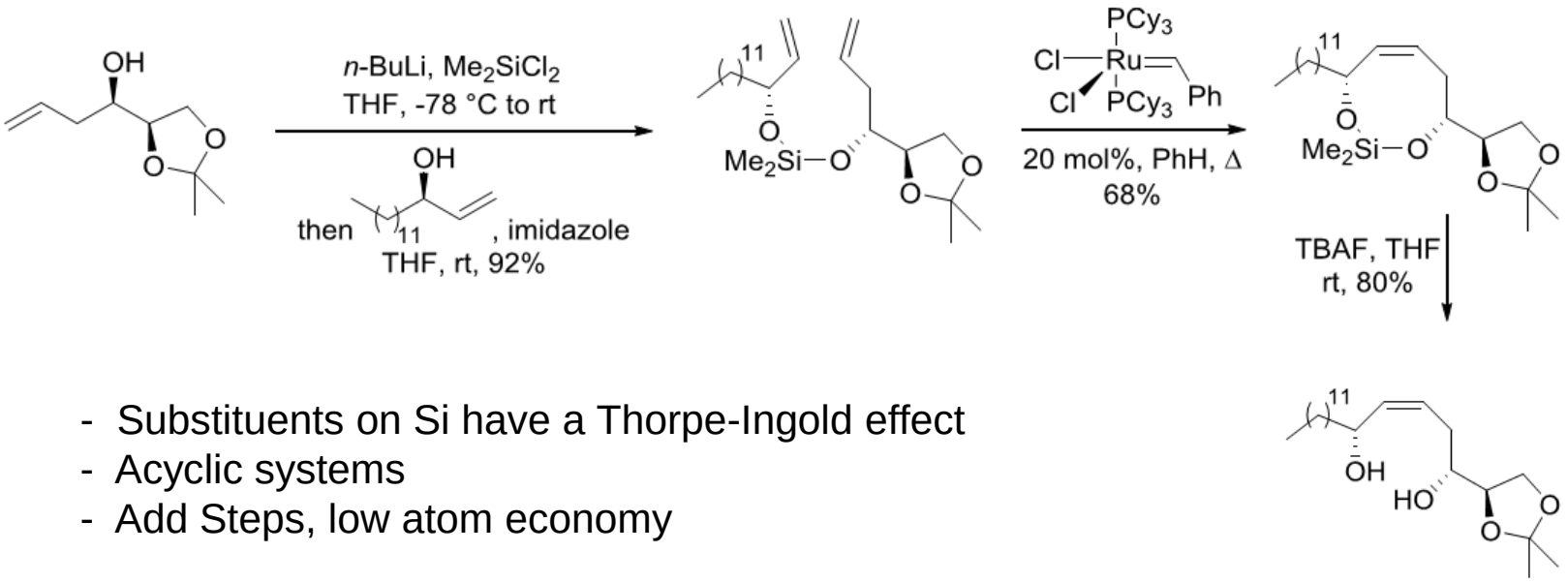
II - Z-selective strategies: Alkynes metathesis/Z-selective hydrogenation

Alkynes metathesis: Molybdenum-based catalysts



J. Heppekausen, R. Stade, R. Goddard, A. Fürstner, *J. Am.Chem. Soc*. **2010**, 132, 11045 – 11057
A. Fürstner *et al*, *Chem. Eur. J*. **2012**, 18, 10281 – 10299

II - Z-selective strategies
Silicon Tethering

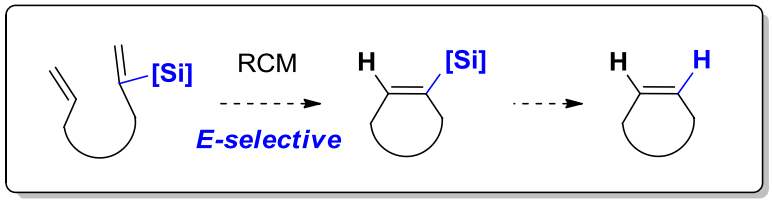


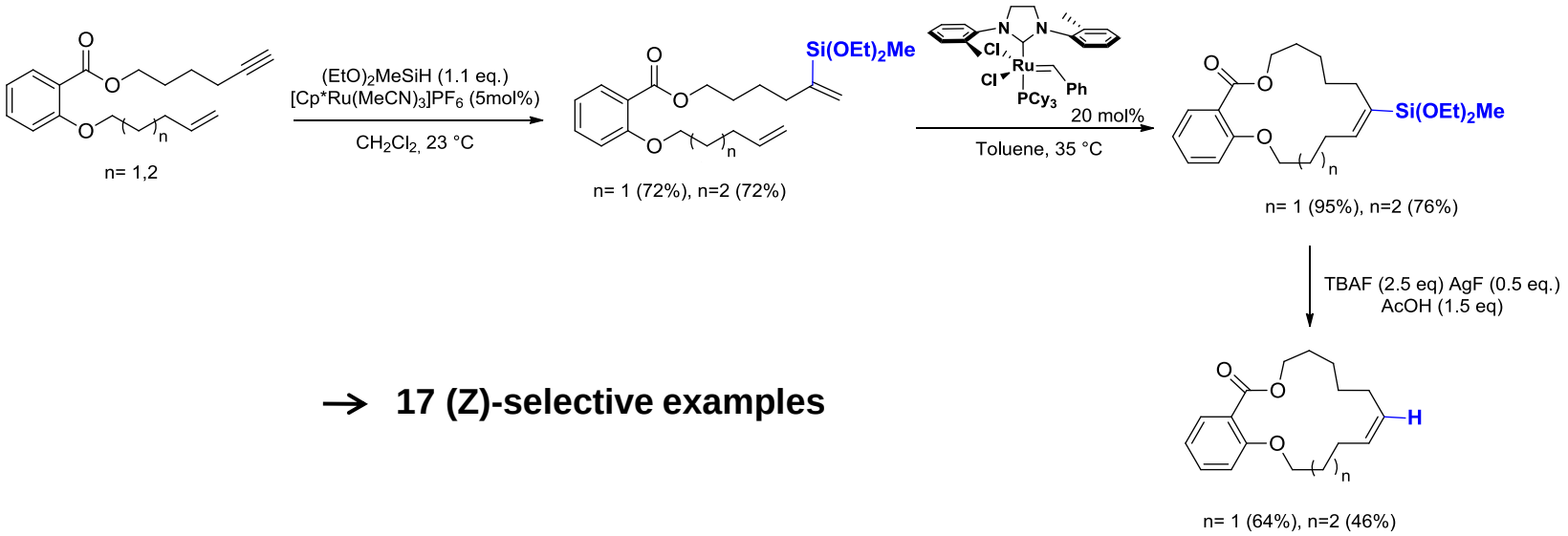
- Substituents on Si have a Thorpe-Ingold effect
- Acyclic systems
- Add Steps, low atom economy

Čusak, A. *Chem. Eur. J*. **2012**, 18, 5800-5824
Van de Weghe, P.; Bourg, S.; Eustache, J. *Tetrahedron* **2003**, 59, 7365-7376.

II - Z-selective strategies

Indirect substrate Control: Removable silyl groups



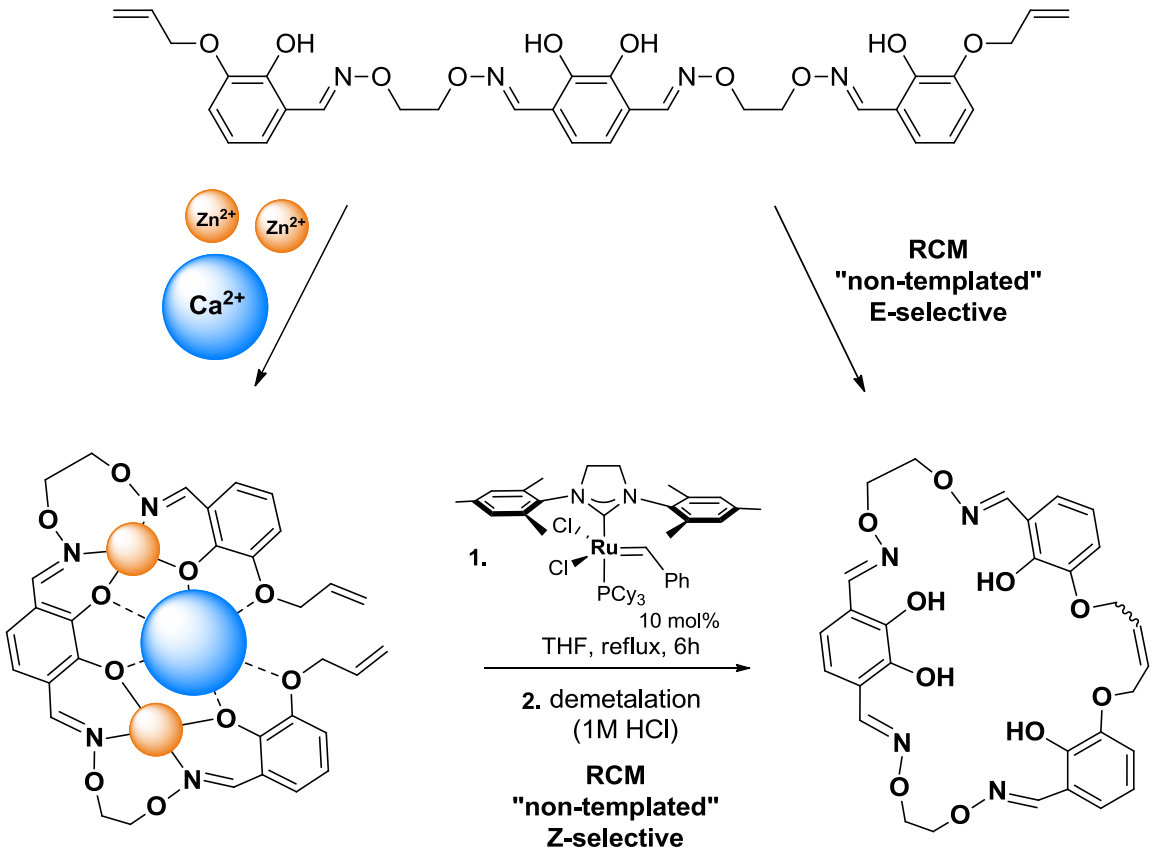


→ **17 (Z)-selective examples**

Y. Wang, M. Jimenez, A. S. Hansen, E.-A. Raiber, S. L. Schreiber, D. W. Young, *J. Am. Chem. Soc.* **2011**, 133, 9196

II - Z-selective strategies

Templated RCM

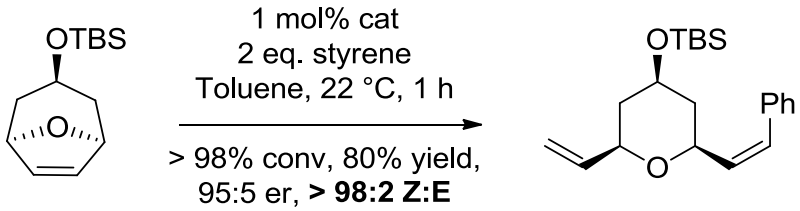


S. Akine, S. Kagiyama, T. Nabeshima, *Inorg. Chem.* **2007**, 46, 9525

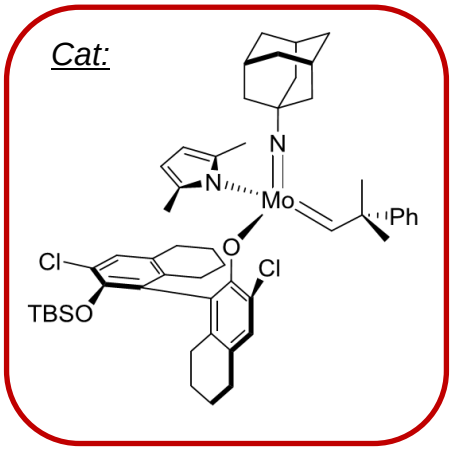
II - Z-selective catalysts

Molybdnemun- and Tungsten-Based catalysts

ROCM



Stereogenic-at-Mo monoaryloxide-pyrrolide (MAP)



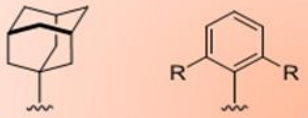
I. Ibrahem, M. Yu, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**,131, 3844.

Z-selective catalysts

Molybdnemun- and Tungsten-Based catalysts

→ **MAP catalyst**

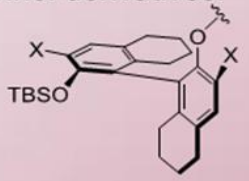
Imido Ligand
- Adamantyl or aryl



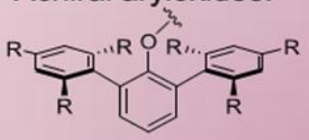
Imidazole Ligand
- With or without Me in 2,5-positions

Alkylidene Ligand
- Bulky group to prevent bimolecular decomposition
- R = CMe_3 or CMe_2Ph

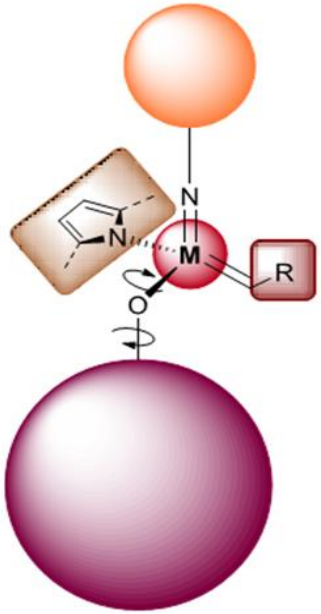
Aryloxide Ligand
- Very bulky to get good Z-selectivity
- Binol derivatives:



- Achiral aryloxides:



- Aryloxy-ligand can freely rotate

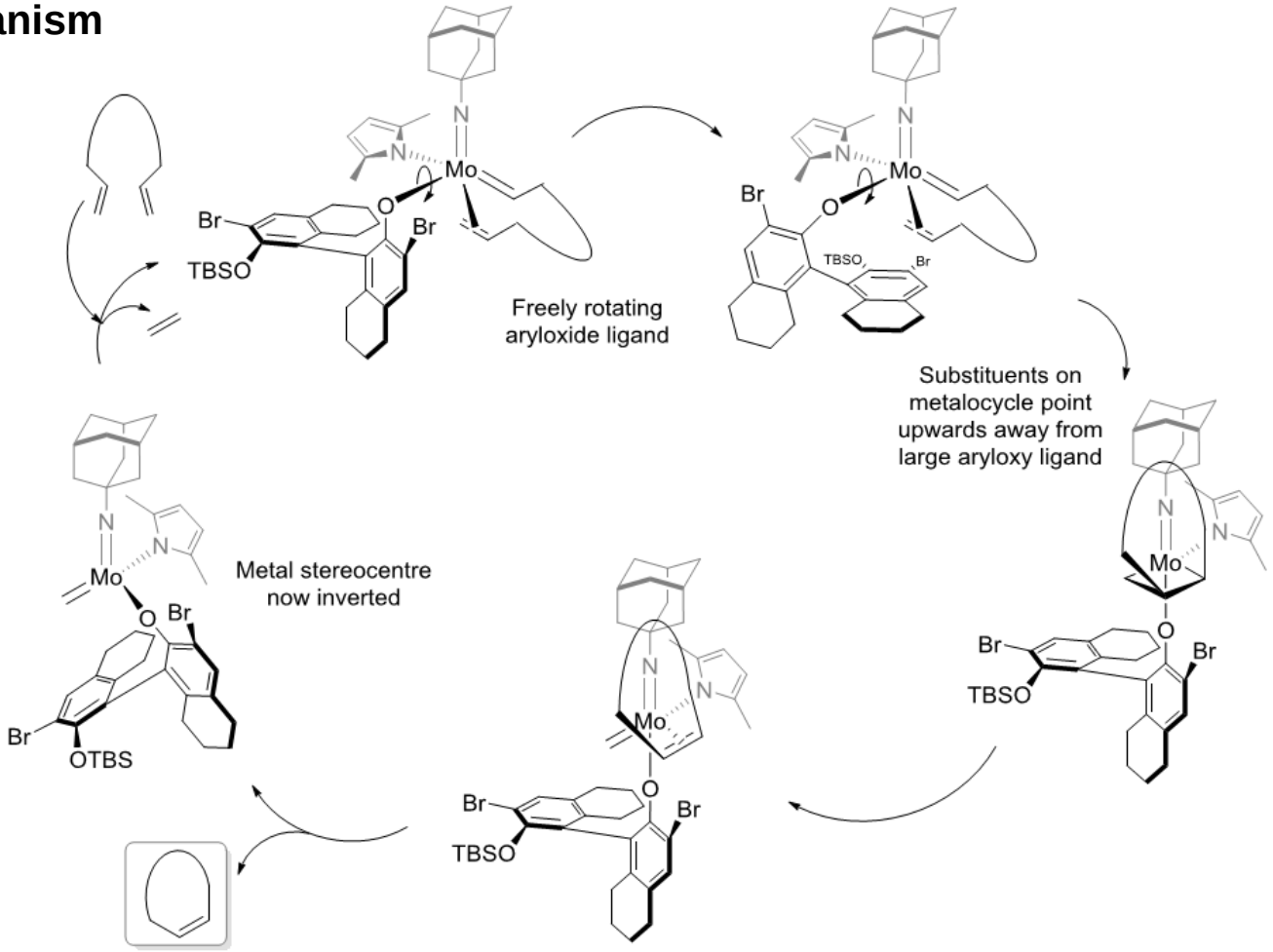


Metal Centre
- Choice of Mo or W
- **Mo**:
  - More active
  - More prone to 2° isomerisation
  - Very air/moisture sensitive
- **W**:
  - Less active, but more selective
  - Less prone to isomerisation
  - Air/moisture tolerant

II - Z-selective catalysts

Molybdnemun- and Tungsten-Based catalysts

Mechanism

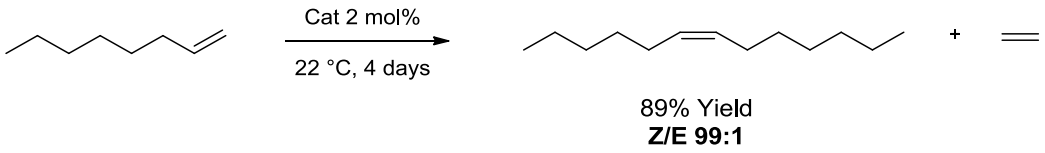


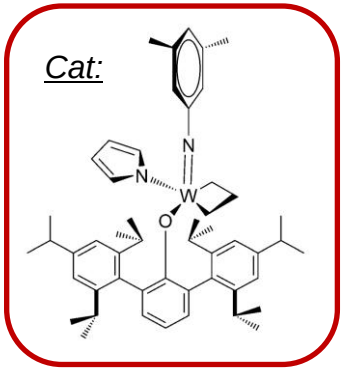
Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, 19, 2726-2740

II - Z-selective catalysts

Molybdnemun- and Tungsten-Based catalysts

Self-metathesis



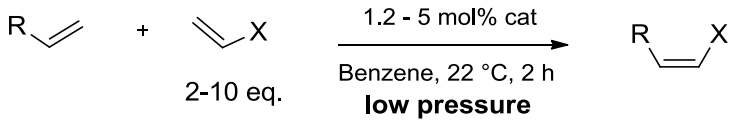


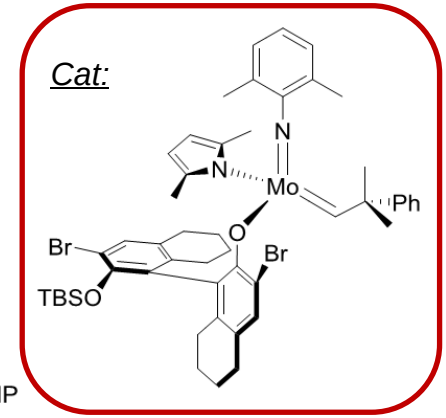
S. C. Marinescu, R. R. Schrock, P. Müller, M. K. Takase, A. H. Hoveyda, *Organometallics* **2011**, 30, 1780.

II - Z-selective catalysts

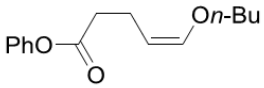
Molybdnemun- and Tungsten-Based catalysts

Cross-metathesis

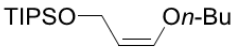




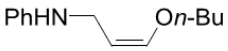
- enol ethers:



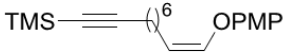
73%yield
(98% Z)



77%yield
(94% Z)

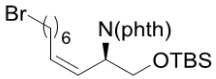


51%yield
(>98% Z)

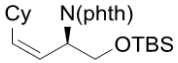


59%yield
(>98% Z)

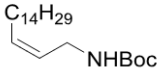
- allylic amides:



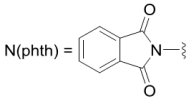
93%yield
(96% Z)



65%yield
(97% Z)



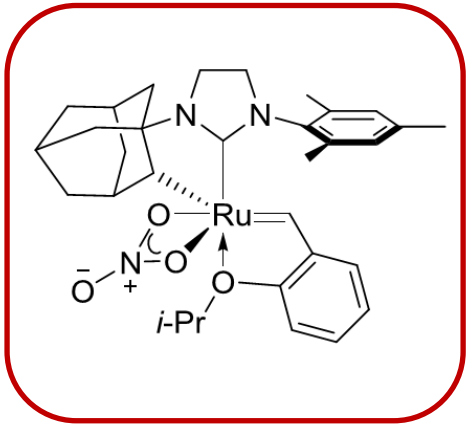
93%yield
(96% Z)

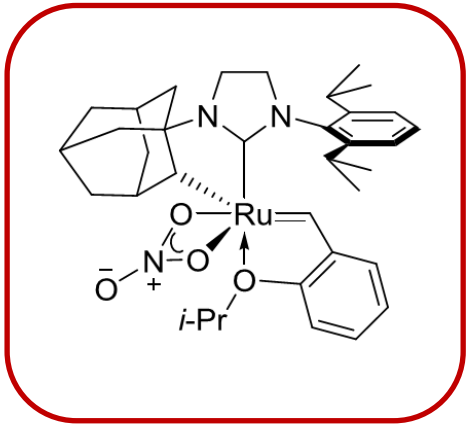


S. J. Meek, R. V. O'Brien, J. Llaviera, R. R. Schrock, A. H. Hoveyda, *Nature* , **2011**, 471, 461

II - Z-selective catalysts

Ruthenium catalysts



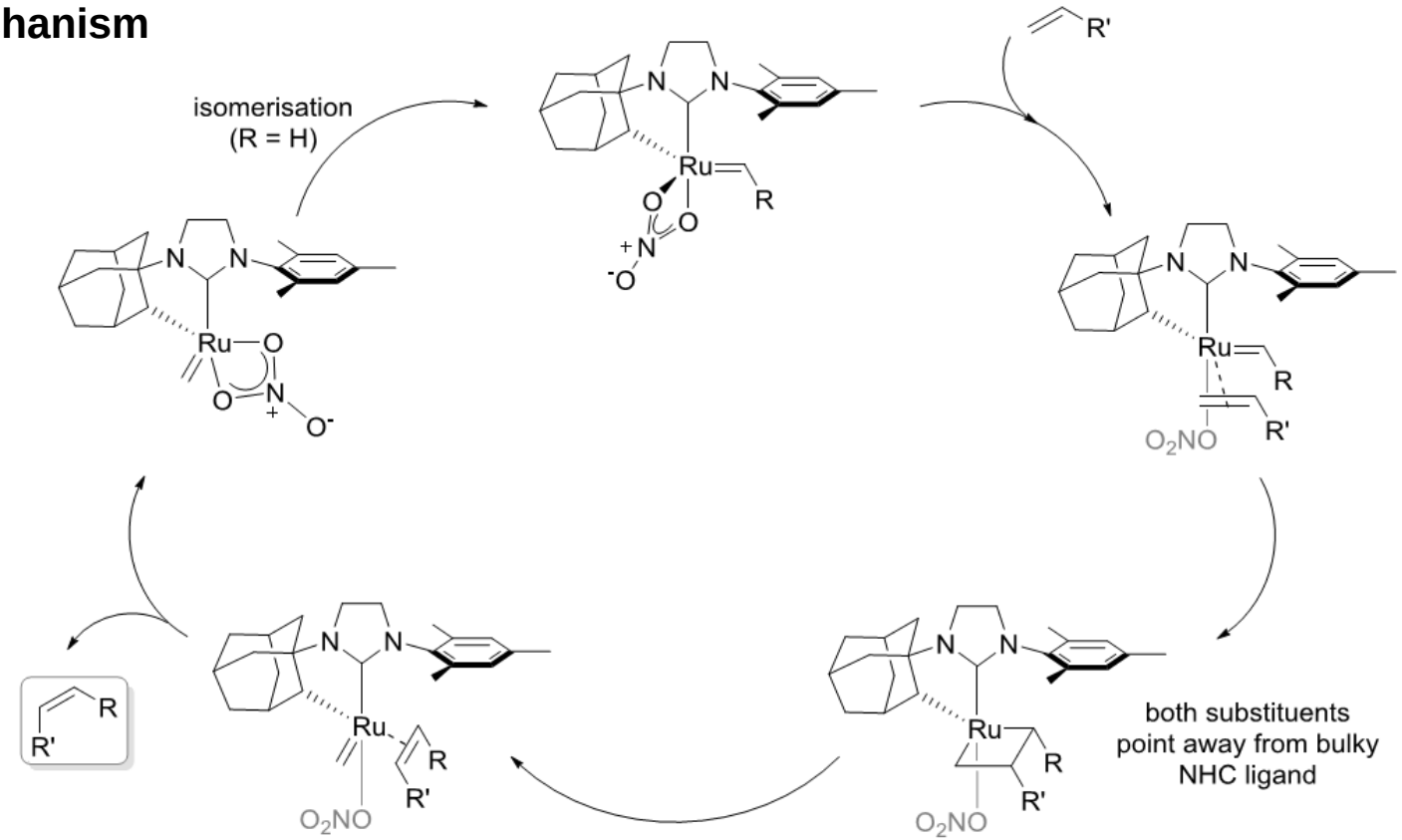


Endo, K.; Grubbs, R. H. *J. Am. Chem. Soc*. **2011**, 133, 8525-8527

Rosebrugh, L. E.; Herbert, M. B.; Marx, V. M.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc*. **2013**, 135, 1276-1279

II - Z-selective catalysts
Ruthenium catalysts

Mechanism

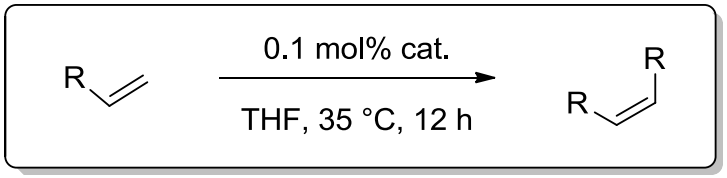


*Dang, Y.; Wang, Z-X.; Wang, X. Organometallics , **2012**, 31, 7222-7234*

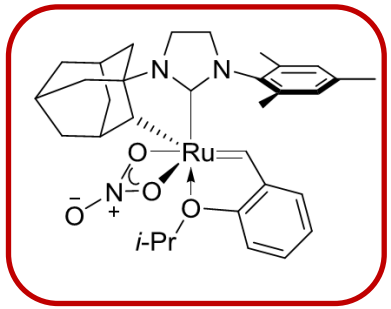
II - Z-selective catalysts

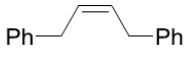
Ruthenium catalysts

Homodimerization

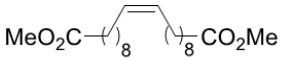


Cat:

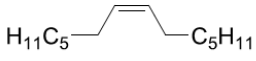




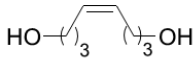
91%yield
(92% Z)



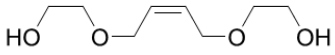
85%yield
(91% Z)



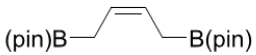
83%yield
(92% Z)



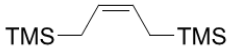
67%yield
(81% Z)



30%yield
(67% Z)



36%yield
(>95% Z)



14%yield
(>95% Z)

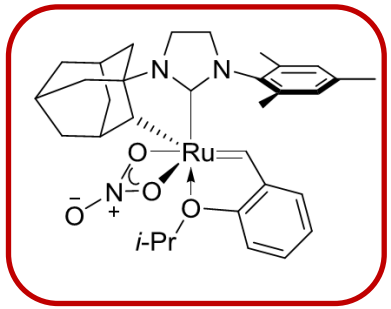
Keitz, B. K.; Endo, K.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* ***2011****,* 133, 9686-9688

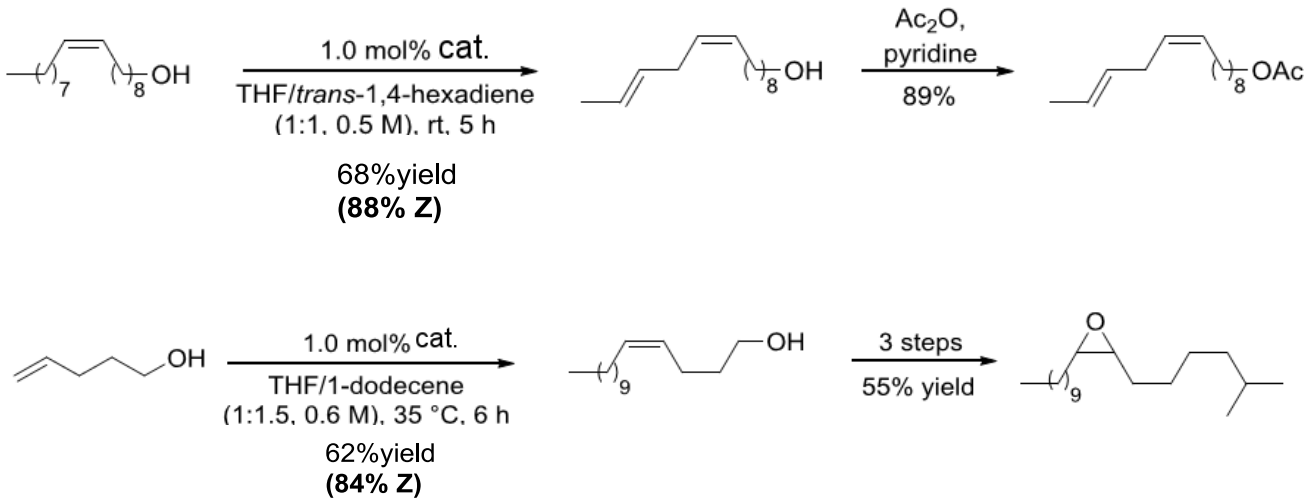
Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs*, R. H. J. Am. Chem. Soc.* ***2012****,* 134, 693-699

II - Z-selective catalysts
Ruthenium catalysts

Cross Metathesis

Cat:



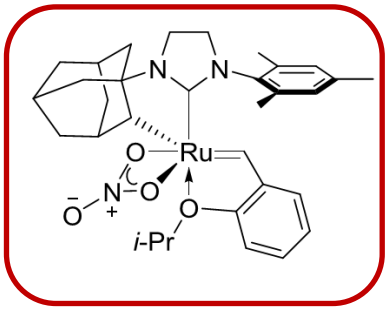


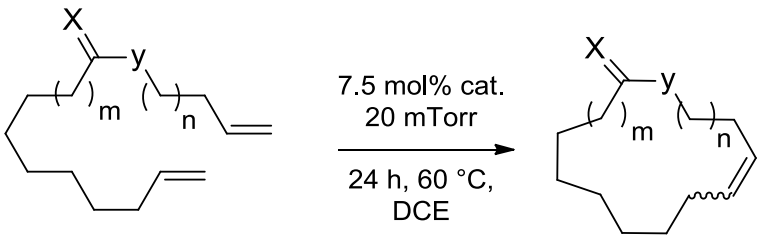
Herbert, M. B.; Marx, V. M.; Pederson, R. L.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2013**, 52, 310-314

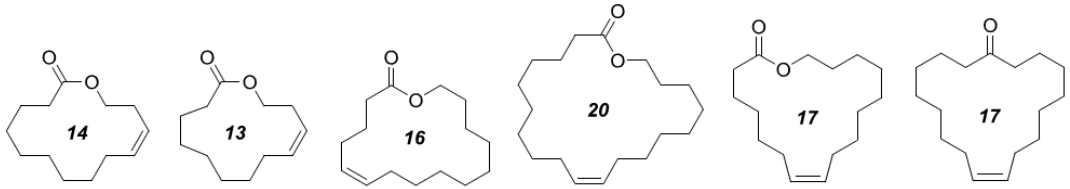
II - Z-selective catalysts
Ruthenium catalysts

RCM

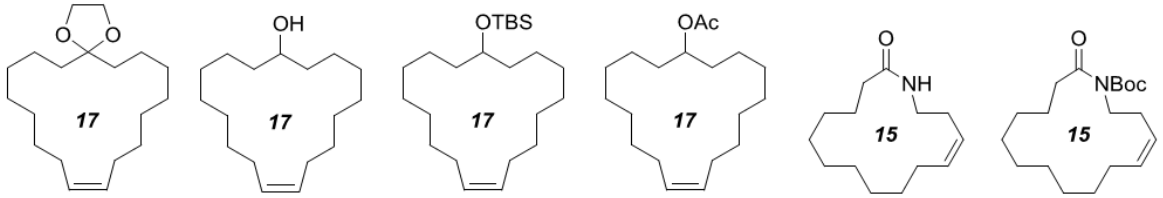
Cat:







58%yield **(85% Z)** | 40%yield **(86% Z)** | 72%yield **84% Z)** | 75%yield **(94% Z)** | 71%yield **(89% Z)** | 50%yield **(68% Z)**



60%yield **(85% Z)** | 56%yield **(65% Z)** | 56%yield **(75% Z)** | 59%yield **(75% Z)** | 30%yield **(84% Z)** | 59%yield **(83% Z)**

Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc*. **2013**, 135, 94-97

II - Z-selective catalysts

Comparing Mo-/W - and Ru- Based Catalysts

Molybdenum/Tungsten	Ruthenium
Much broader reaction profile, more developed field	Still limited to fairly simple examples
Mo: air and water sensitive **W**: can be water and air tolerant	Catalysts tend to be less sensitive
Need higher catalyst loadings (0.1 – 10 mol%)	Generally use lower catalyst loadings (0.01-5 mol%)
More ‘designable’, can make logical modifications	Less well-defined structure-property relationships
5-step synthesis of catalyst	1-3 step synthesis of catalyst

Overview

I- Introduction

- The early days
- Non-selective catalysts

II- Z-selectivity

- Z-selective methodologies : The early steps
- Z-selective strategies
  - Alkyne metathesis/Z-selective hydrogenation
    - Alkyne metathesis / Introduction
    - Alkyne metathesis / Catalysts
  - Silicon Tethering
  - Indirect substrate Control: Removable silyl groups
  - Templated RCM
- Z-selective catalysts
  - Molybdnemun- and Tungsten-Based catalysts
  - Ruthenium catalysts

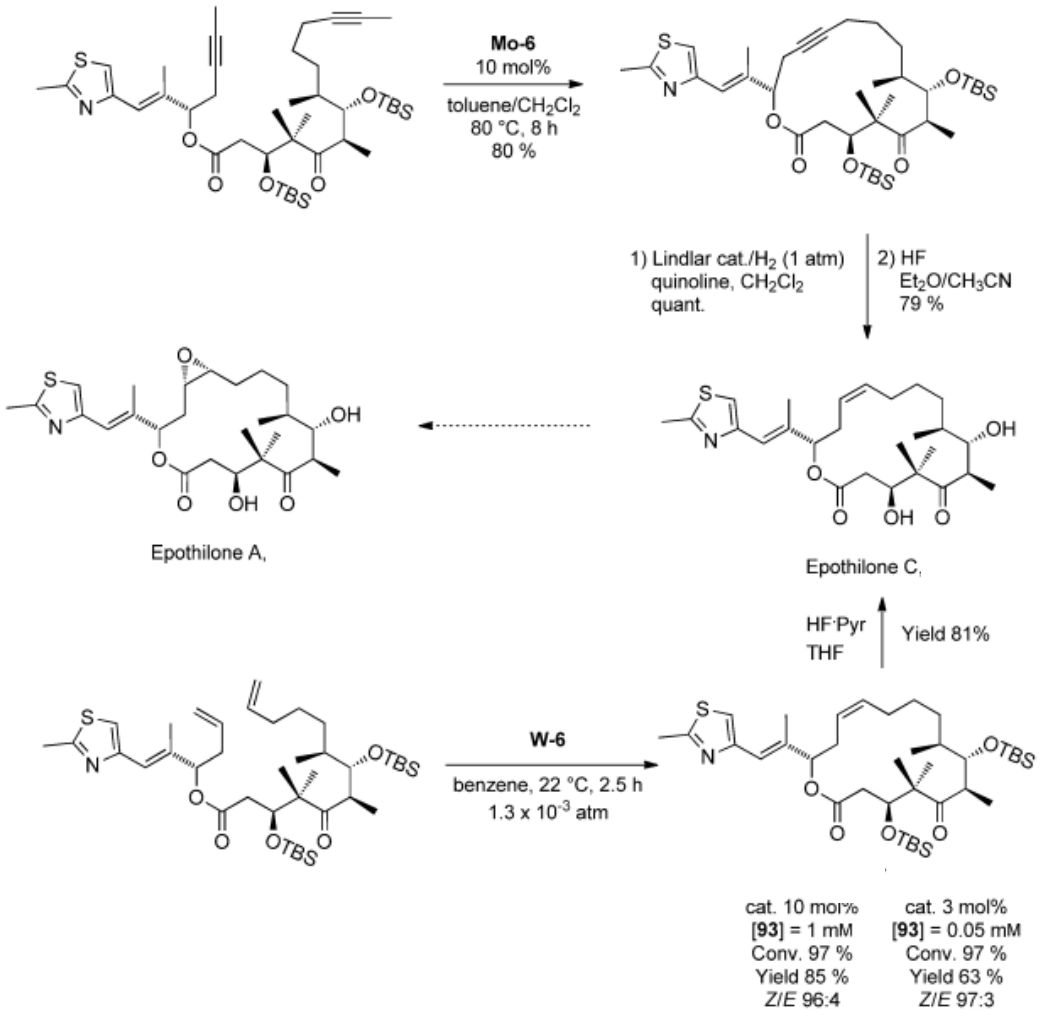
III - Selected Total Synthesis Applications

- Concise total synthesis of epothilone A and C
- Total synthesis of Nakadomarin A
- Concise total synthesis of epothilone D
- Key step en route to oximidine III

Conclusion

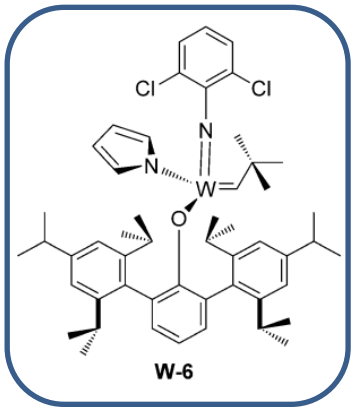
IV - Selected Total Synthesis Applications

Concise total synthesis of epothilone A and C



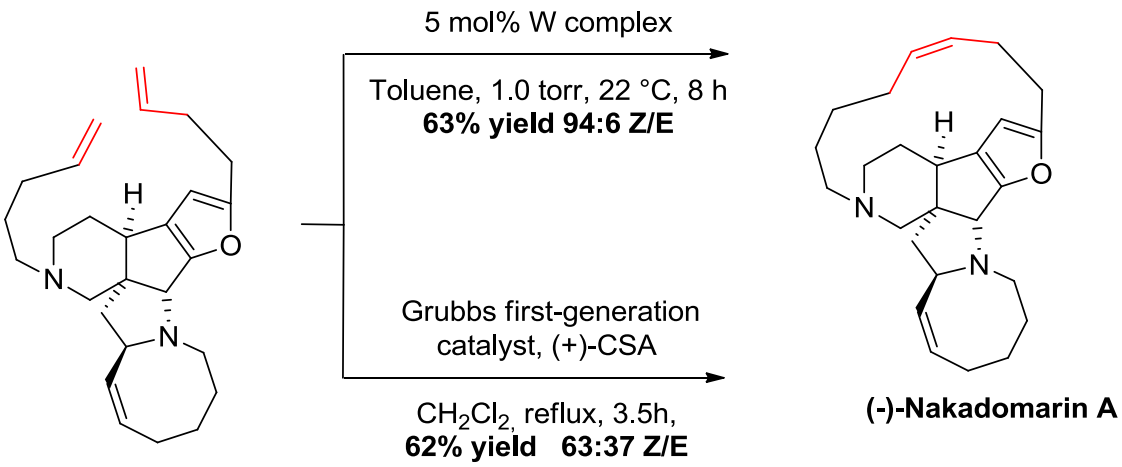
Mo-6 =

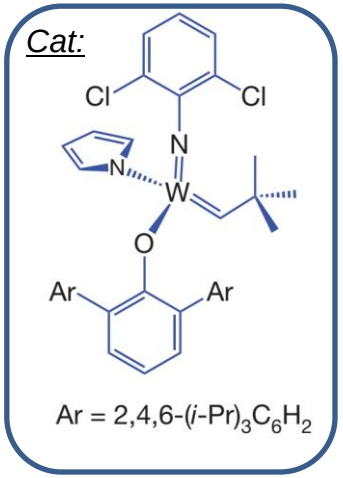
[**Mo**{(tBu)(3,5-dimethylphenyl)N}$_3$]



IV - Selected Total Synthesis Applications

Total synthesis of Nakadomarin A

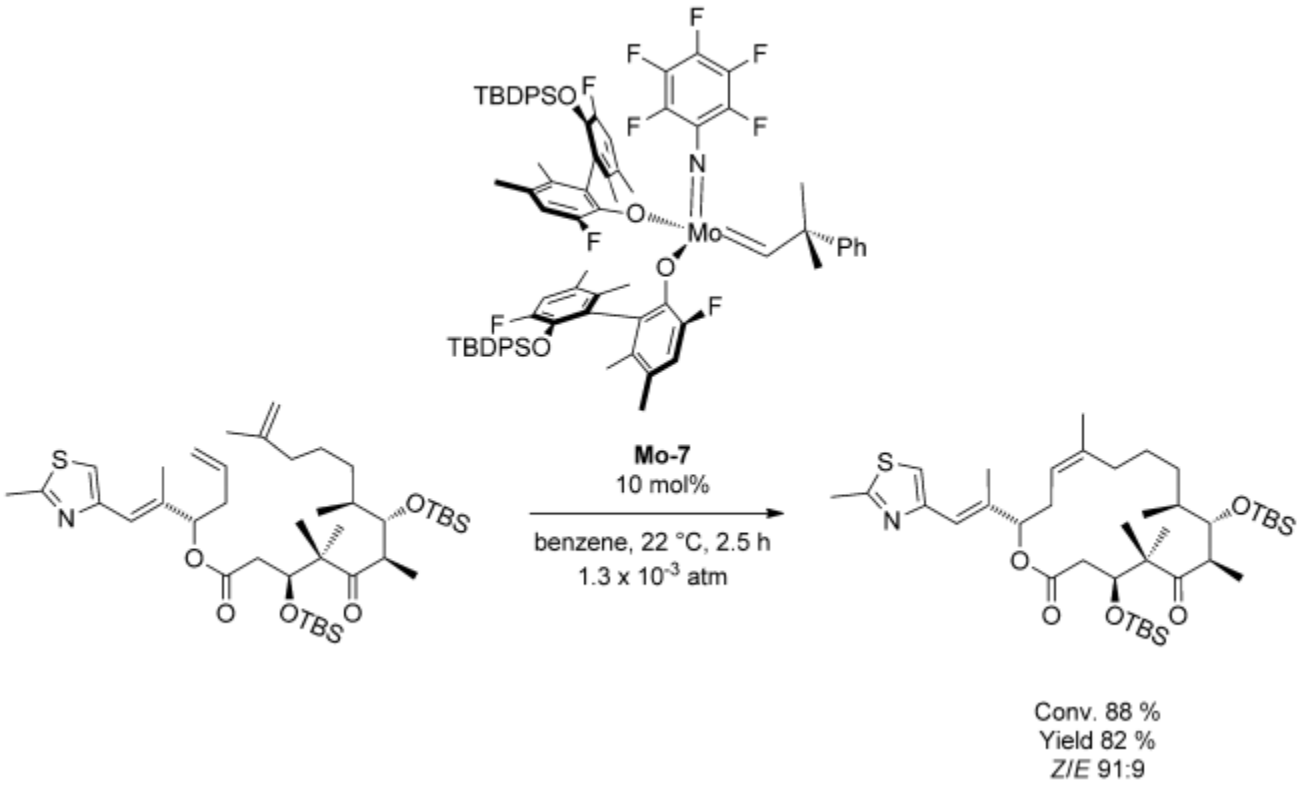




M. Yu, C. Wang, AF. Kyle, P Jakubec, D.J. Dixon, R.R. Schrock, A.H.Hoveyda. *Nature*. **2011** 479, 88-93

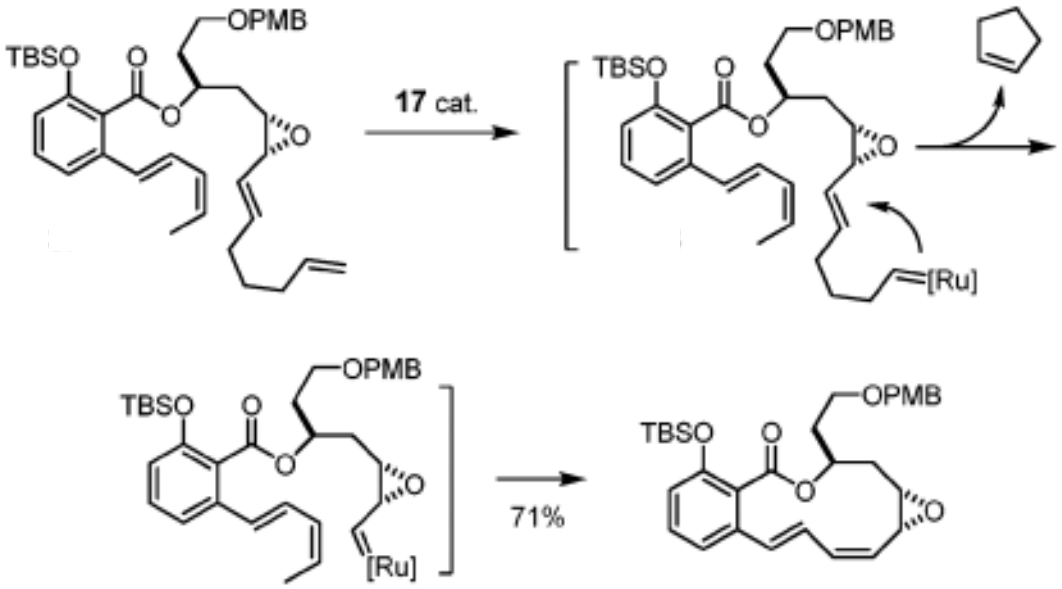
IV - Selected Total Synthesis Applications

Concise total synthesis of epothilone D



IV - Selected Total Synthesis Applications

Key step en route to oximidine III



X. Wang, E. J. Bowman, B. J. Bowman and J. A. Porco, Jr., *Angew. Chem., Int. Ed.*, **2004**, 43, 3601

Conclusion

- Z-selective olefin metathesis represents a **significant challenge**

- **Various** options Z-alkenes metathesis **strategies**: from more ‘traditional’ indirect methods to **powerful** new catalytic systems

- **Limitation** of the catalyst-controlled methodology: difficulties in accessing catalysts and lack of examples

Conclusion

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- Limitation of the catalyst-controlled methodology: difficulties in accessing catalysts and lack of examples

Thank you for you attention.