

# Olefin Metathesis Catalysts for the Synthesis of Molecules and Materials

December 8, 2005

Stockholm, Sweden

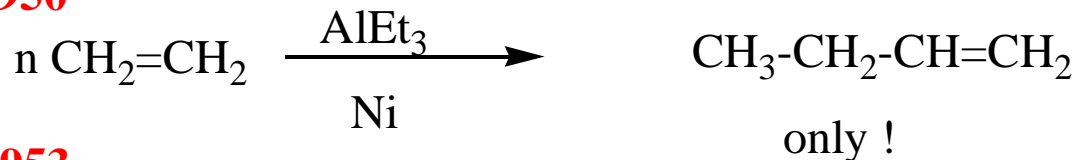
# New Polyethylene

Ziegler --MPI in Mulheim

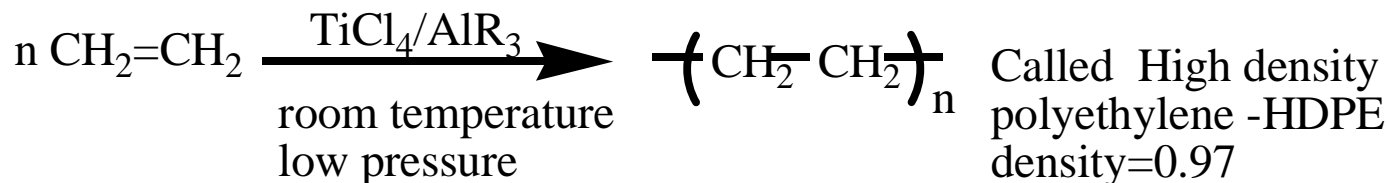
1940's- war years



1950<sup>+</sup>



1953



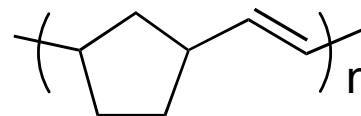
Crystalline - Milk bottles

K. Ziegler and G. Natta, Nobel Prize 1963

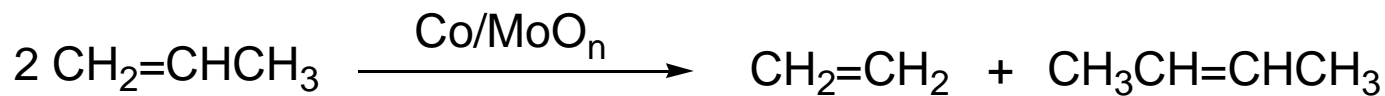
# Discovery of a New Reaction



Polymer containing unsaturation-  
unexpected for an addition polymer



Truett, et al, *J. Am. Chem. Soc.*, **1960**, 2337



Three carbons

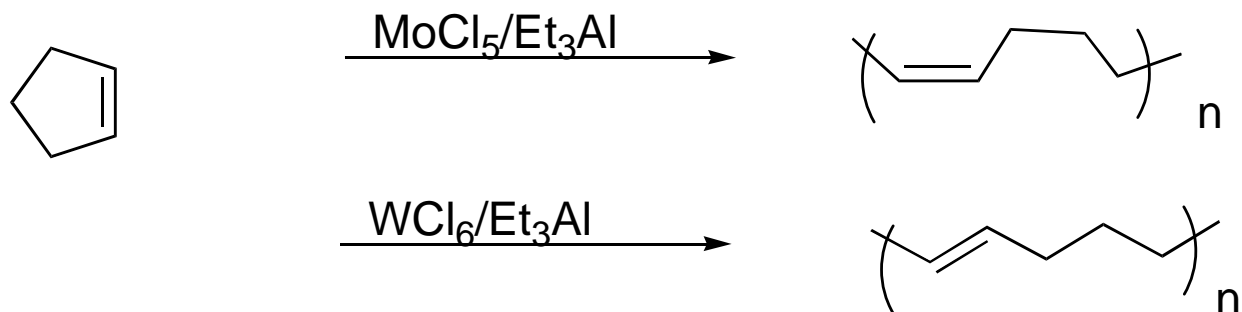
Two carbons

Four carbons

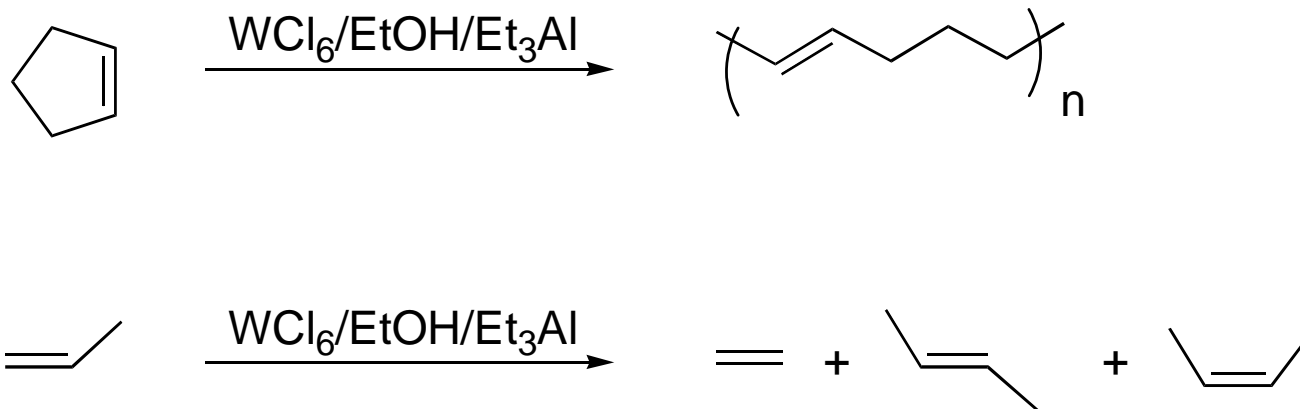
Heterogeneous Catalyst

R. L.. Banks and G. C. Bailey, *I & EC Product Research and Development*, **1964**, 170

# Metathesis Discovery

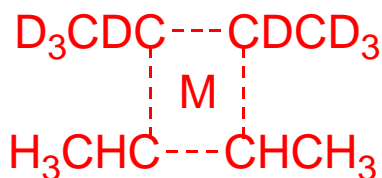
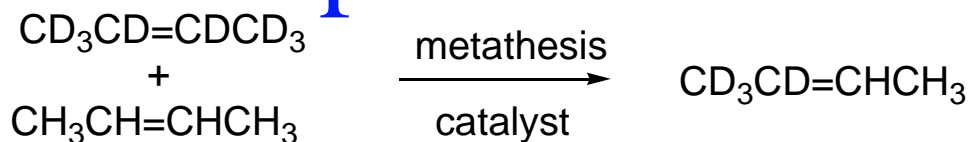


Natta, et. al. J. Polymer Sci., Polymer Lett. 1964, B2, 349



Calderon, Chen, Scott, Tetrahedron Letters, 1967, 3327

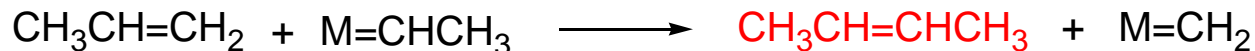
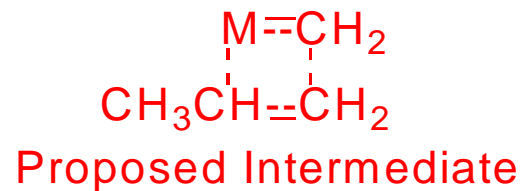
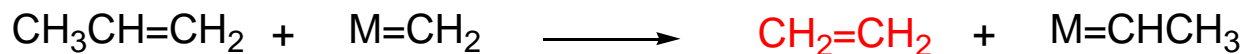
# Proposed Mechanisms



Proposed intermediate

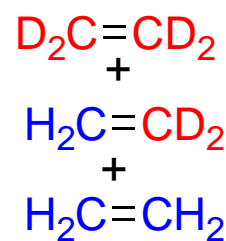
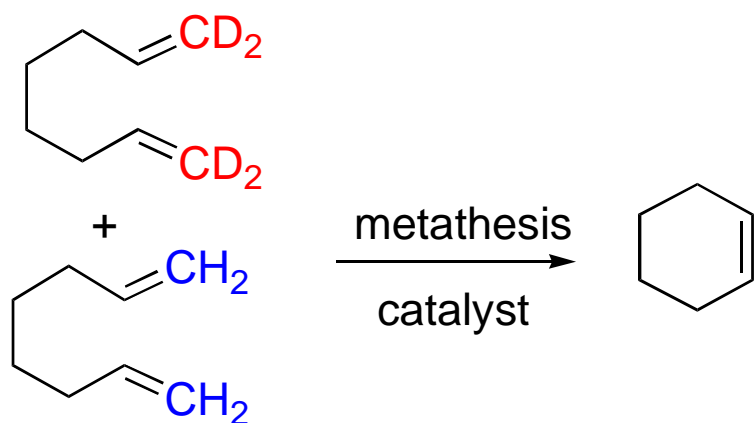
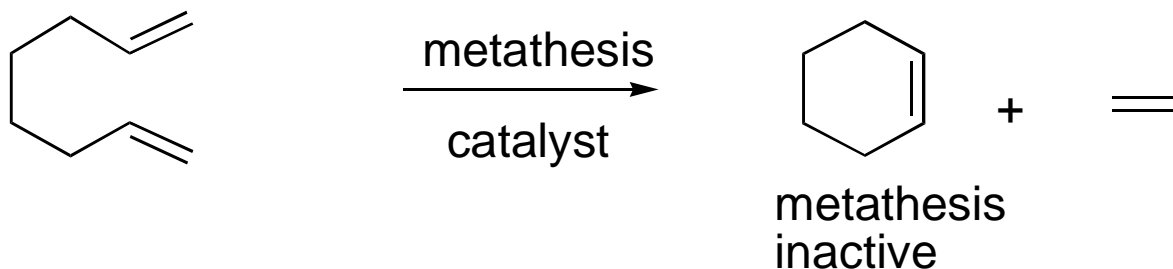
$\text{CD}_3\text{CH}=\text{CHCH}_3$
$\text{CD}_3\text{CD}=\text{CDCH}_3$
$\text{CD}_3\text{CH}=\text{CHCD}_3$
$\text{CH}_3\text{CD}=\text{CDCH}_3$
Not Observed

N. Calderon, E. A. Olfsead, J. P. Ward, W. A. Judy, K. W. Scott, *J. Am. Chem. Soc.*, **1968**, *90*, 4133



J. L. Herisson, Y. Chauvin *Makromol. Chemie*, **1971**, *141*, 162 Based on cross metathesis  
T. J. Katz, J. McGinnis, *J. Am. Chem. Soc.*, **1975**, *97*, 1592

# Mechanistic Study



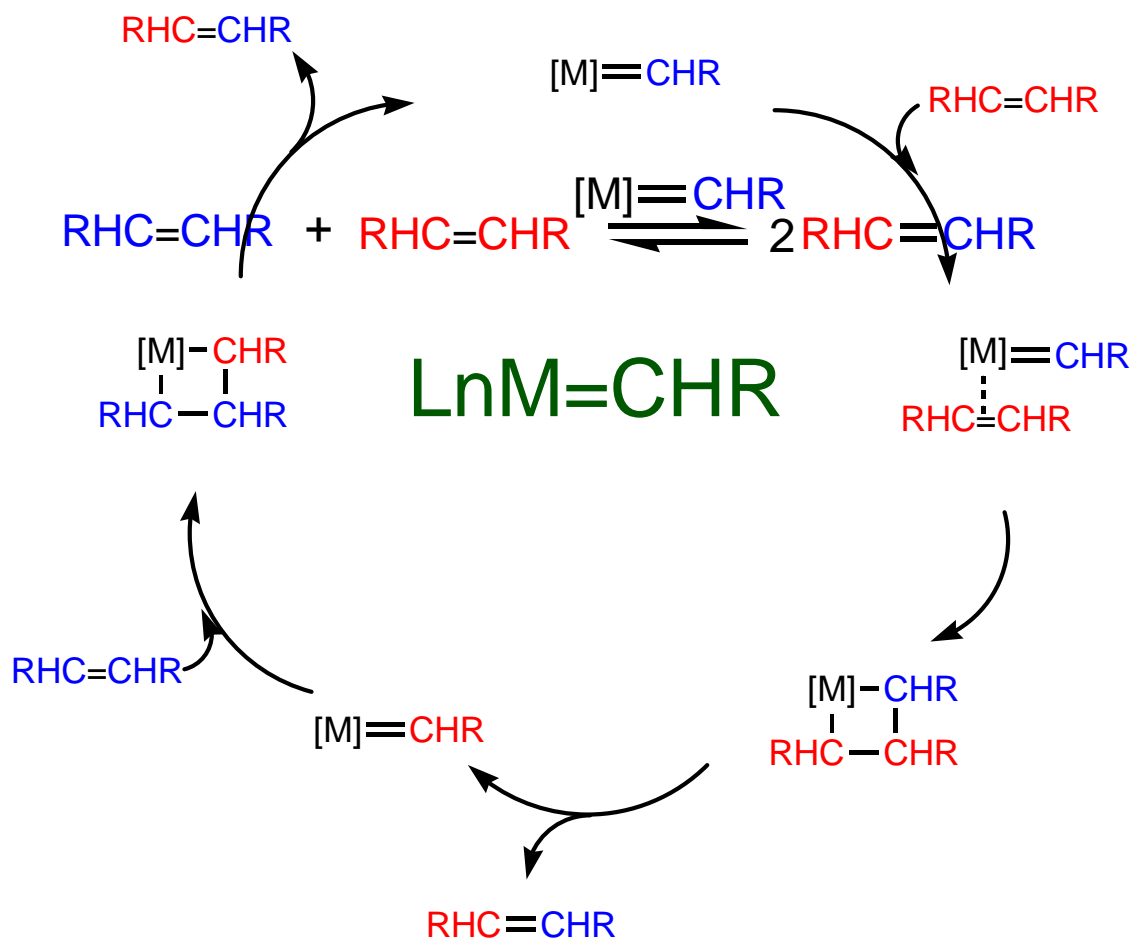
predicted Ratio	
Chauvin	pairwise
1	1
2	0 (1.6)
1	1



**OBSERVED**

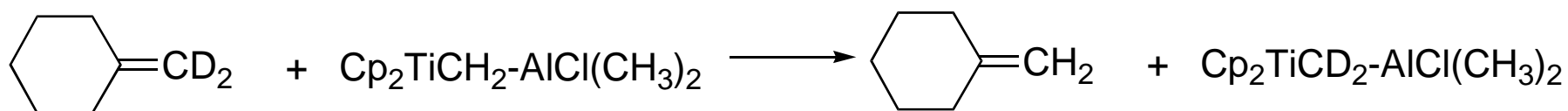
R. H. Grubbs, P. L. Burk and D. D. Carr, *J. Am. Chem. Soc.* **1975**, 97, 3265.  
 T. J. Katz and R. Rothchild, *J. Am. Chem. Soc.* **1976**, 98, 2519.

# Olefin Metathesis Mechanism



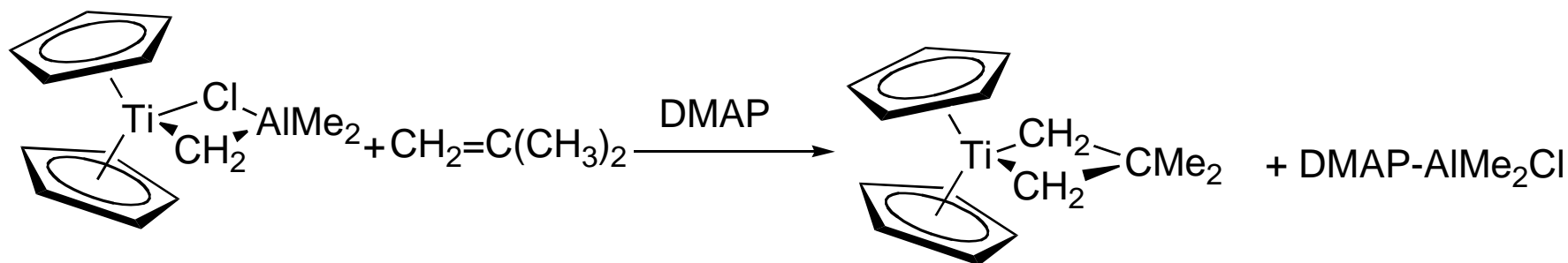
# Carbene Catalysts

Demonstration of Exchange between Metal Methylene and an Olefin



F.N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, 100, 3611

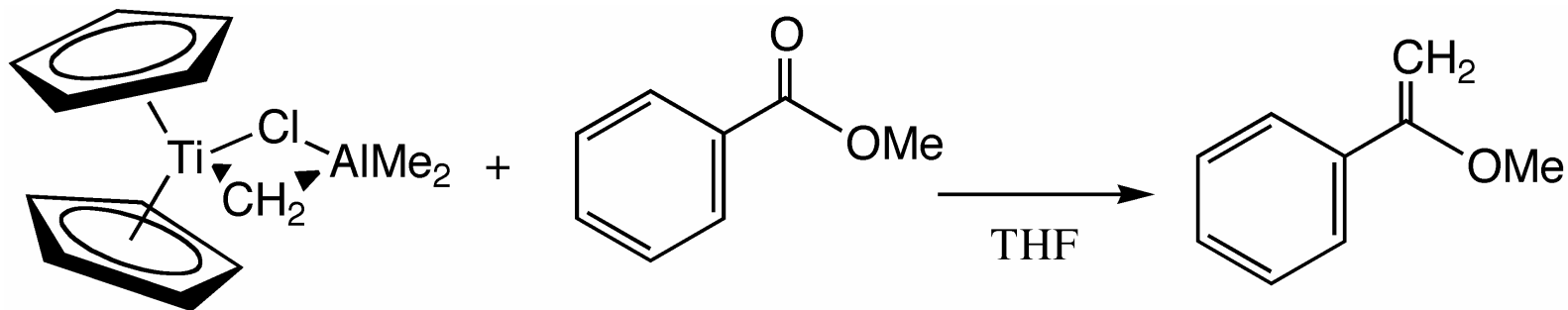
Isolation of Metallacycle in Active Metathesis System



T. R. Howard, J. B. Lee and R. H. Grubbs, *J. Am. Chem. Soc.*, **1980**, 102, 6876.



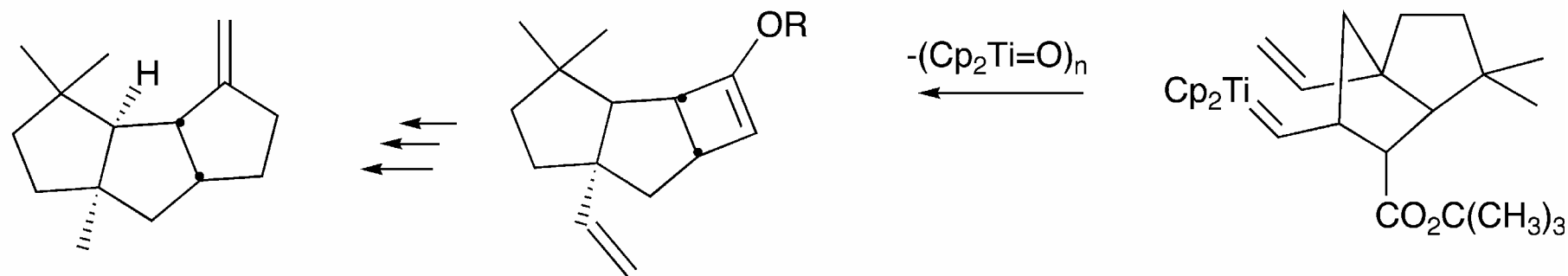
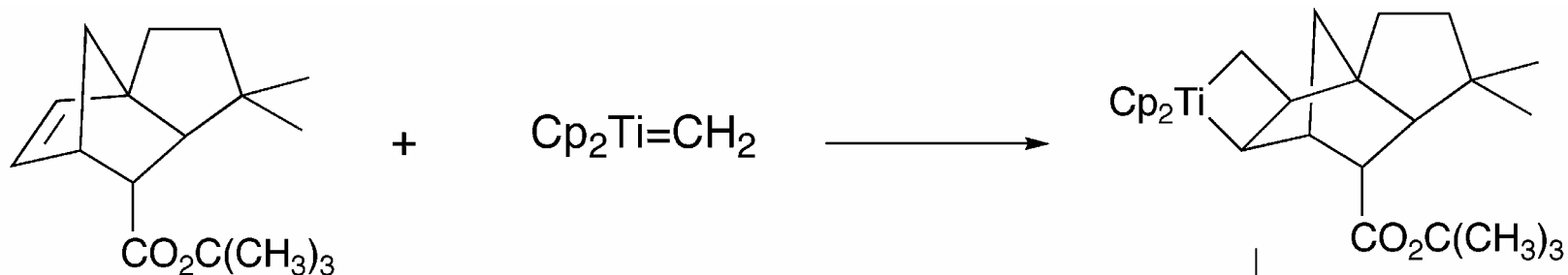
# Tebbe Reagent



S. H. Pine, R. Zahler, D. A. Evans and R. H. Grubbs, *J. Am. Chem. Soc.* **1980**, *102*, 3270.

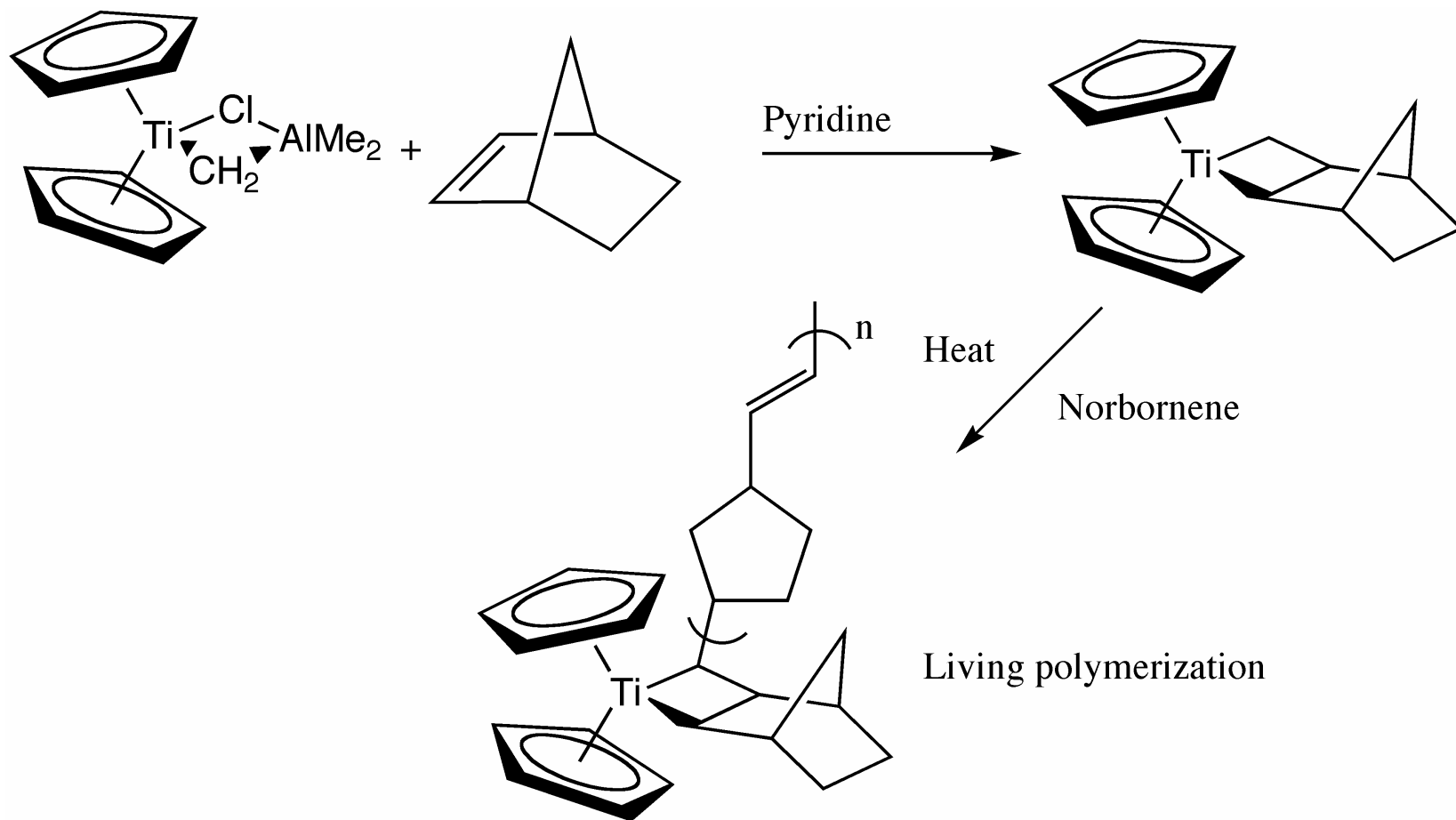
Metal Alkylidenes in Organic Synthesis

# Tebbe Reagent in Synthesis

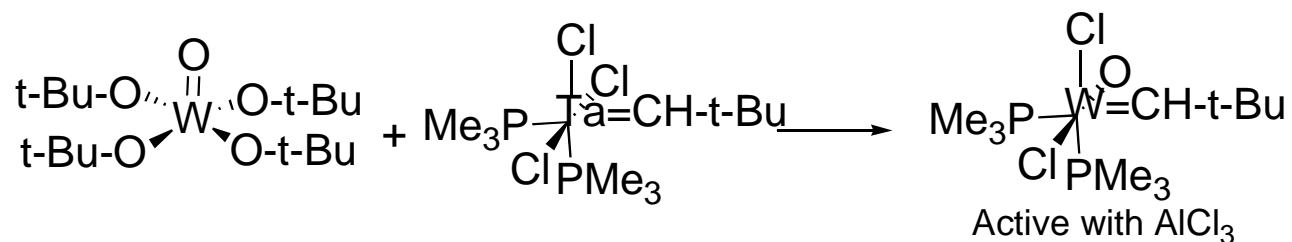


$\Delta^{(9,12)}$ -Capnellene

# Living ROMP Polymers

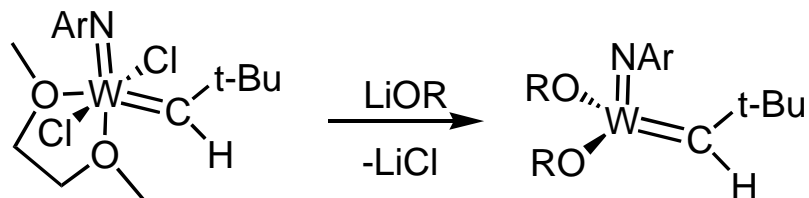


# Schrock Alkylidenes



with terminal olefins  $\text{W}=\text{CH}_2$  complex observed

R. R. Schrock, S. Rockluge, J. Wengrovius, G. Rupprecht, J. Fellmann, *J. Mol. Catal.* **1980**, 8, 73.



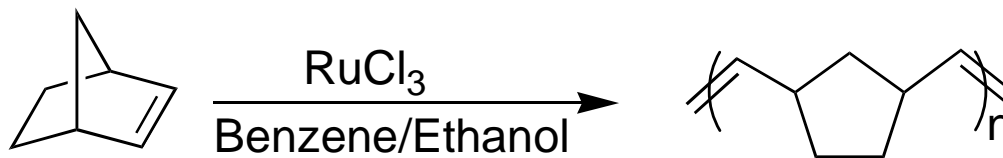
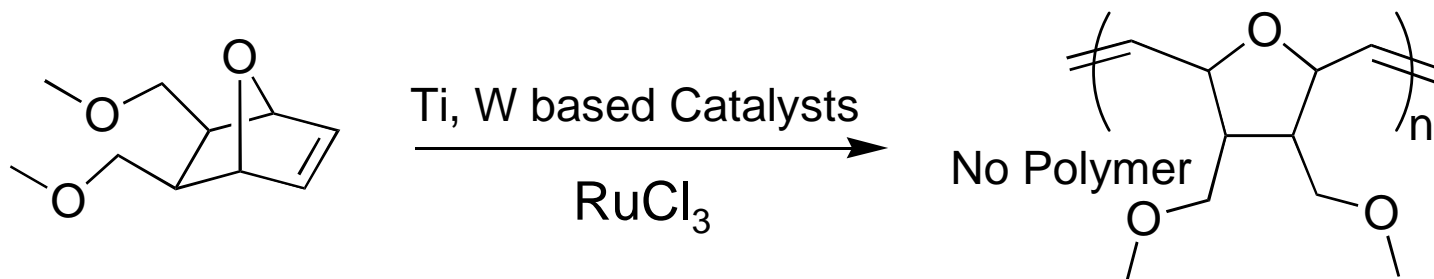
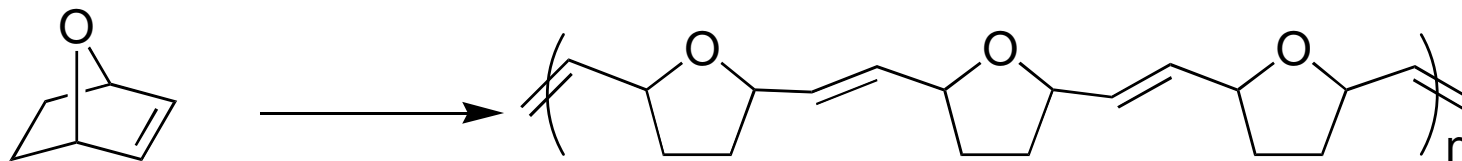
Activity depends on R  
 $[(\text{CF}_3)_2\text{CH}_3]\text{CO}^- \gg (\text{CH}_3)_3\text{CO}^-$  also Mo Analog

R.R.Schrock, R. T. DePue, J. Feldman, C. J. Schaverien, J. C. Deqan, A. H. Liu, *J. Am. Chem. Soc.* **1988**, 110, 1423

(Osborn and Basset also made Active W catalysts)

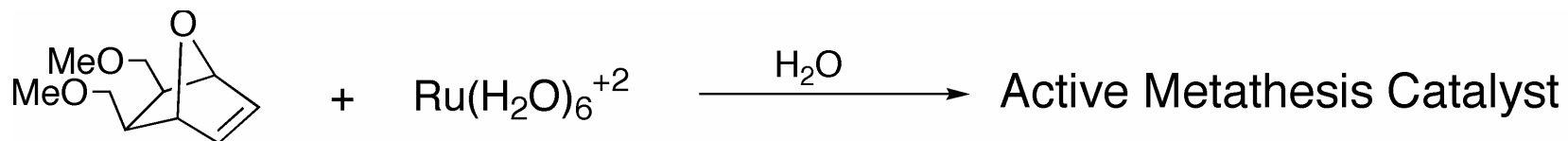
# The Ruthenium Story

# Synthesis of an Ionophore



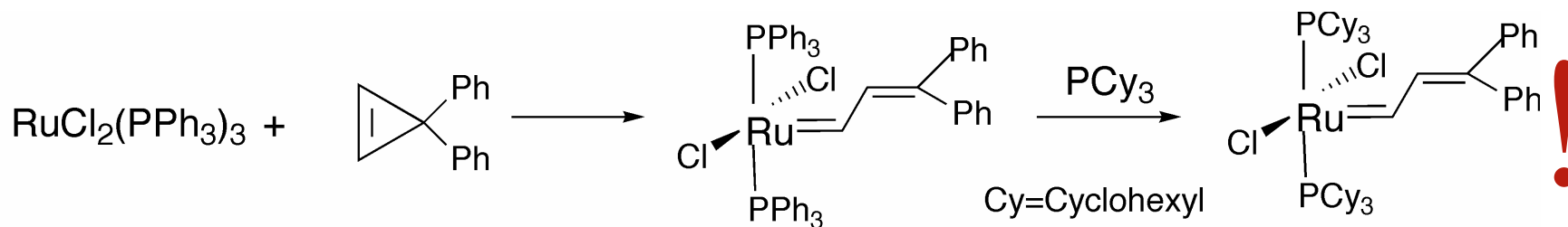
F. W. Michelotti, W. P. Keaveney, *J. Poly. Sci., Part A*, **1965**, 895

# Ruthenium Catalyst Synthesis



B. M. Novak and R. H. Grubbs, *J. Am. Chem. Soc.* **1988**, *110*, 7542-7543

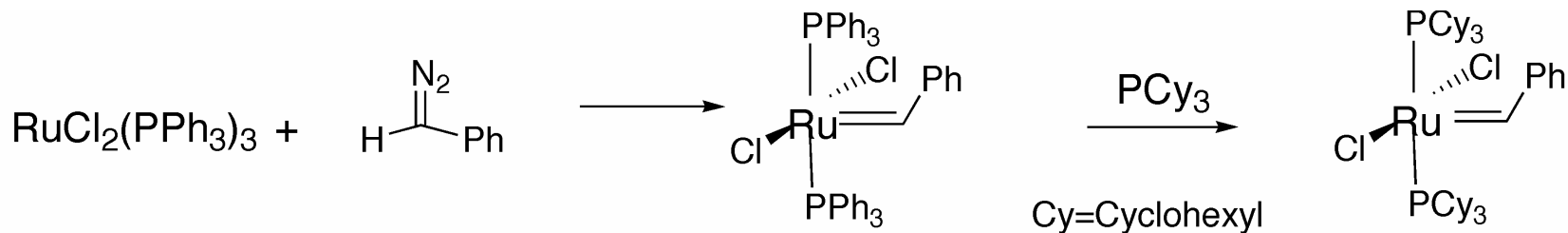
Ill defined, highly active, little initiation



S. T. Nguyen, L. K. Johnson, R. H. Grubbs, and J. W. Ziller, *J. Am. Chem. Soc.* **1992**, *114*, 3974-3975

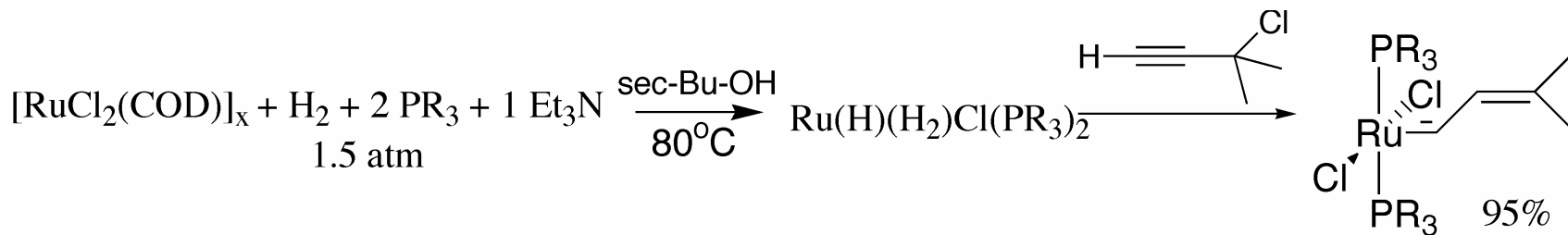
Well defined, good activity, 100mg/week

# Ruthenium Catalyst Synthesis Large Scale



P. Schwab, M. B. France, J. W. Ziller, and R. H. Grubbs, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2039-2041

High activity, Scale up to 15 kg/week, Mike Giardello



T. E. Wilhelm, T. R. Belderrain, S. N. Brown, and R. H. Grubbs, *Organometallics* **1997**, 16(18), 3867-3869.

One Pot, 2 days, scales easily, > 15 kg in 50 gal reactor



# Periodic Table of Elements

IA																	0
1 H																2 He	
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg	IIIB	IVB	VB	VIB	VII B	VII		IB		IB	13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 Y	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba	57 La*	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra	89 Ac*	104 Rf	105 Ha	106	107	108	109	110								

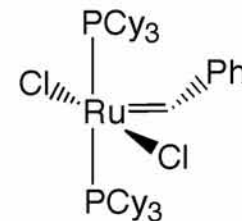
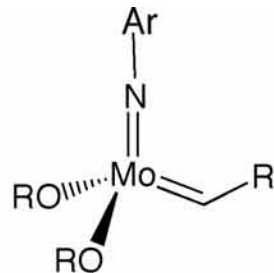
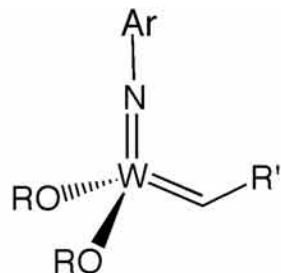
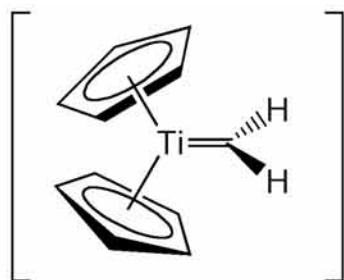
\*Lanthinide Series

58	59	60	61	62	63	64	65	66	67	68	69	70	Lu
Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu

\*Actinide Series

90	91	92	93	94	95	96	97	98	99	100	101	102	Lr
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

# Metal-Centered-Functional Group



**Titanium**

**Tungsten**

**Molybdenum**

**Ruthenium**

Acids

Acids

Acids

**Olefins**

Alcohols, Water

Alcohols, Water

Alcohols, Water

Acids

Aldehydes

Aldehydes

Aldehydes

Alcohols, Water

Ketones

Ketones

**Olefins**

Aldehydes

Esters, Amides

**Olefins**

Ketones

Ketones

**Olefins**

Esters, Amides

Esters, Amides

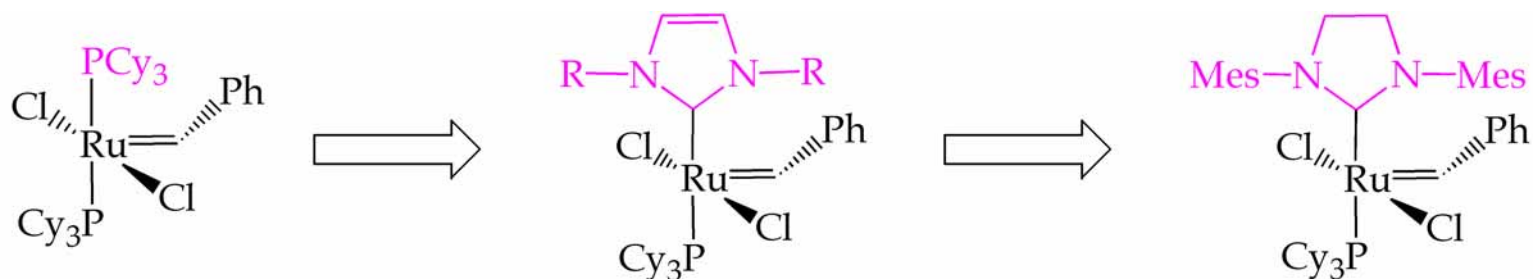
Esters, Amides

*functional group tolerance*

Activity

Increasing  
order of  
reactivity

# Catalyst Developments at Caltech



And Nolan and Herrmann



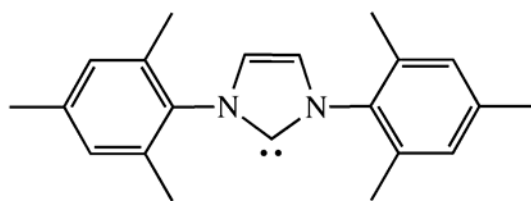
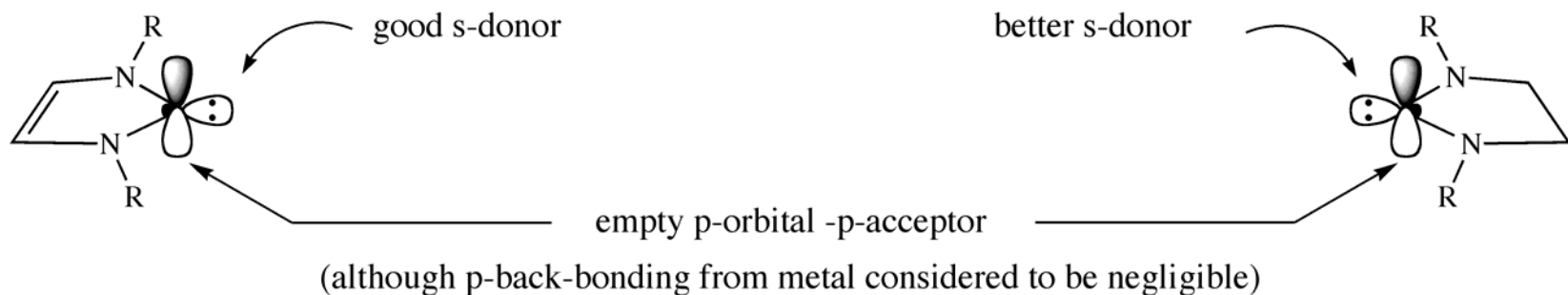
**NHC catalysts are more active for RCM and ROMP (by 10<sup>2</sup>-10<sup>3</sup>)**

Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903.

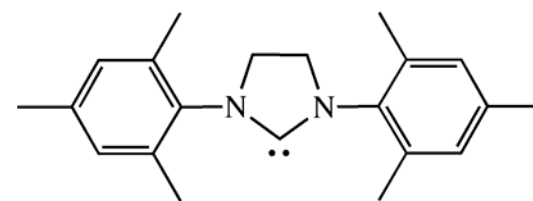
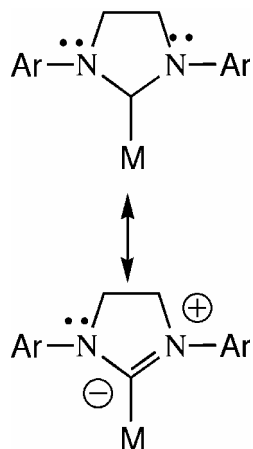
# N-Heterocycle Carbene Ligands

*Singlet carbenes (as in N-Heterocyclic Carbenes)*



IMes

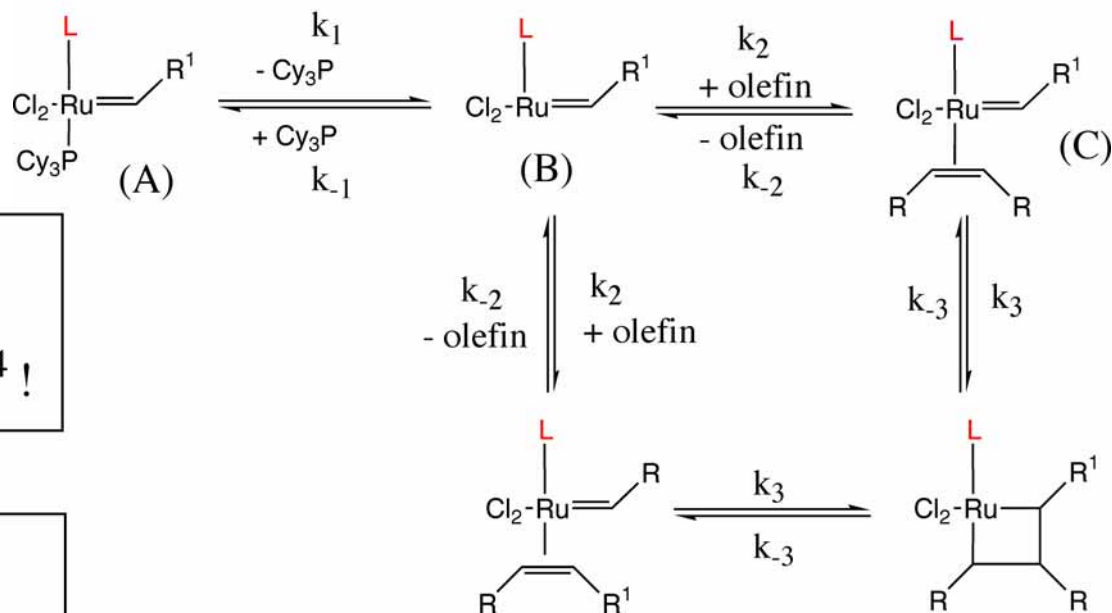
1,3-dimesitylimidazol-2-ylidene



H<sub>2</sub>IMes

1,3-dimesityl-4,5-dihydroimidazol-2-ylidene

# Mechanism



$L = \text{PCy}_3$

$$k_1 (\text{rel}) = \sim 10^2$$

$$k_2/k_{-1} (\text{rel}) = \sim 10^{-4} !$$

$L = \text{H}_2\text{IMes}$

$$k_1 (\text{rel}) = 1$$

$$k_2/k_{-1} (\text{rel}) = 1$$

At steady state

$$\text{Rate} = \frac{k_1 k_2 [\text{A}] [\text{=} ]}{k_{-1} [\text{P}] + k_2 [\text{=} ]}$$

$$k_{-1} [\text{P}] \gg k_2 [\text{=} ]$$

$$\text{Rate} = k_1 \left[ \frac{k_2}{k_{-1}} \right] [\text{A}] \left[ \frac{[\text{=} ]}{[\text{P}]} \right]$$

$$k_{-1} [\text{P}] \ll k_2 [\text{=} ]$$

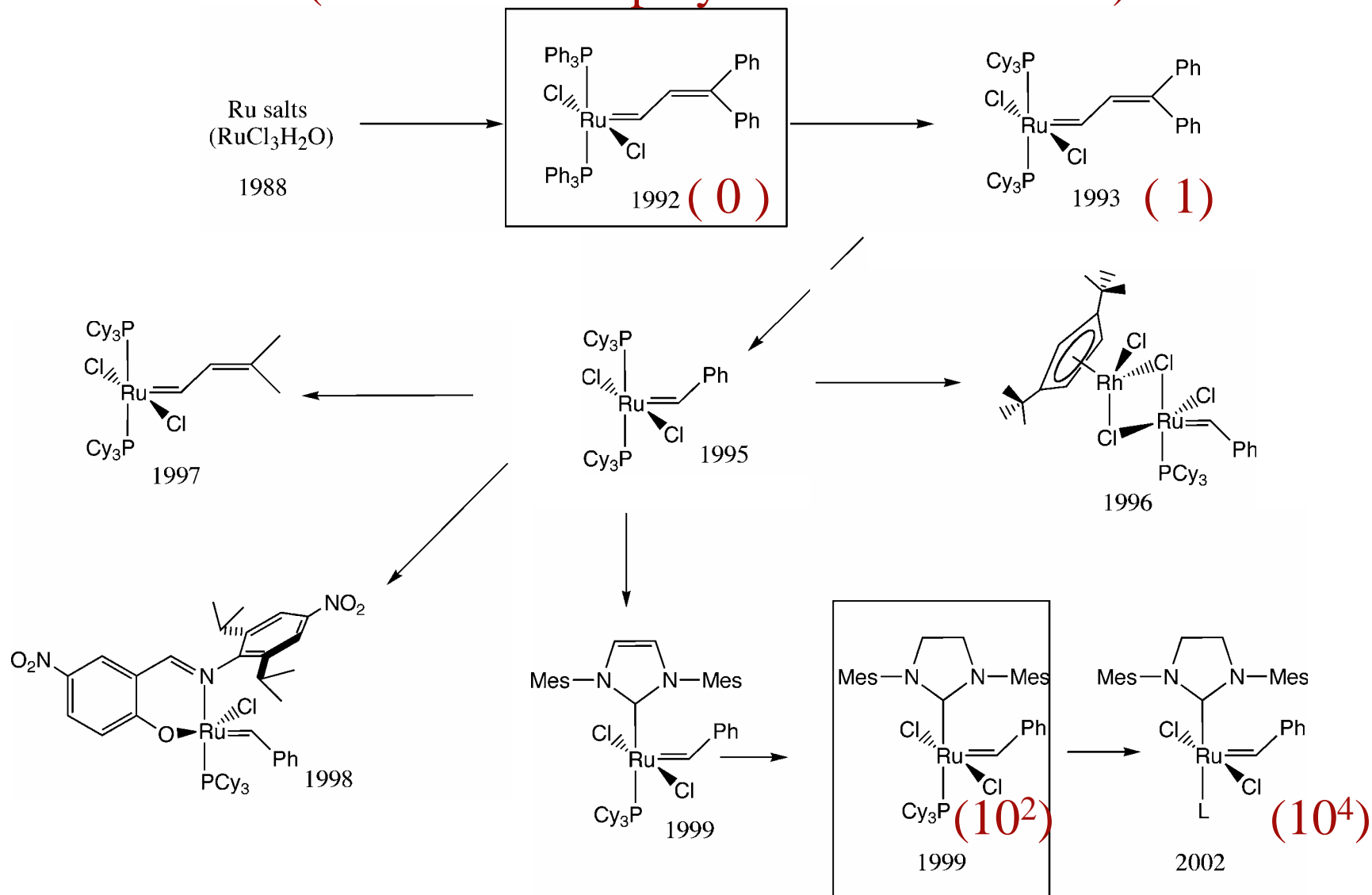
Saturation

$$\text{Rate} = k_1 [\text{A}]$$

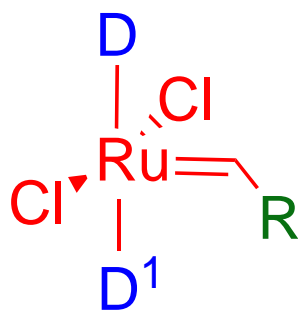
Eric Dias  
Melanie Sanford  
Jen Love

# Ru Catalysis Evolution at Caltech

(relative rate of polymerization of COD)



# Uses and Applications Resulting from Stable, Tolerant Catalysts

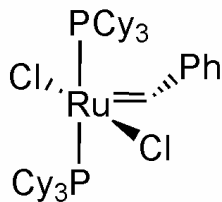


D=2 electron donor

General Catalyst Structure

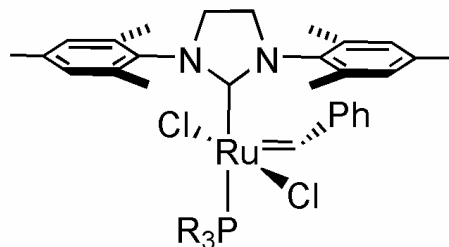
# Commercial Ru Catalysts

## First Generation

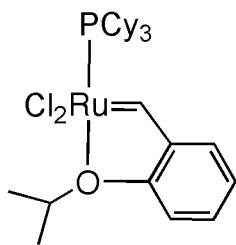


1. Kintically controled products (E:Z)
2. Selective for alkyl substuted double bonds

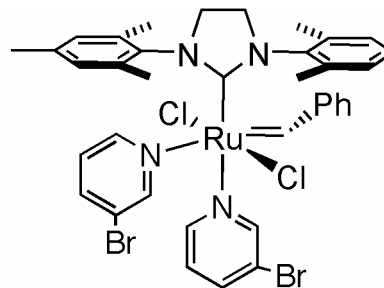
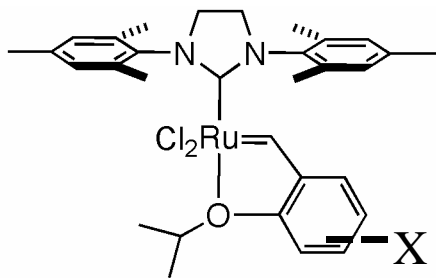
## Second Generation



1. Thermodynamically Control of E:Z
2. Reacts with electron deficient double bonds



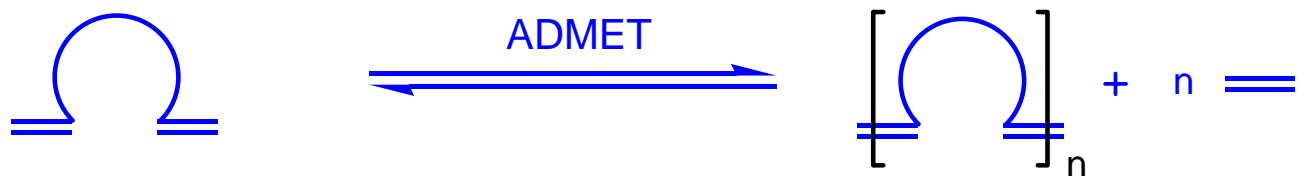
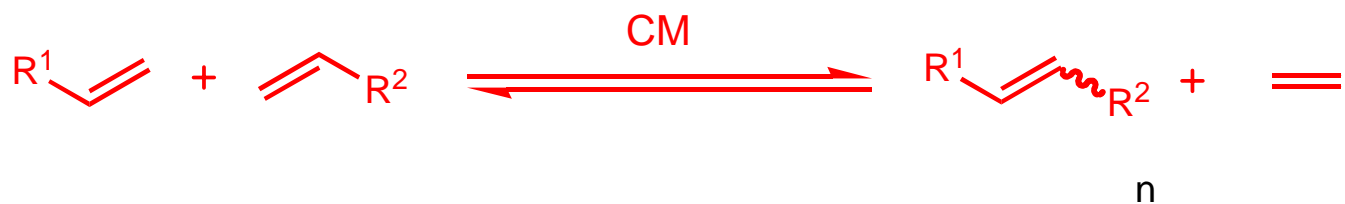
1. Slow initiation
2. Thermally more stable
3. Phosphine free (Hoveyda)



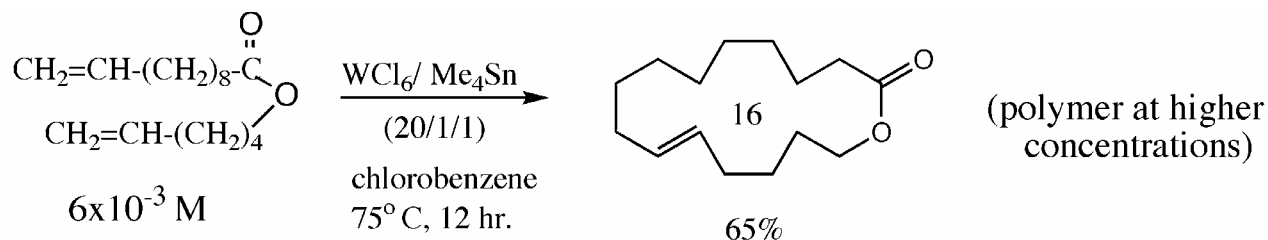
1. Rapid initiation
2. Less thermally stable



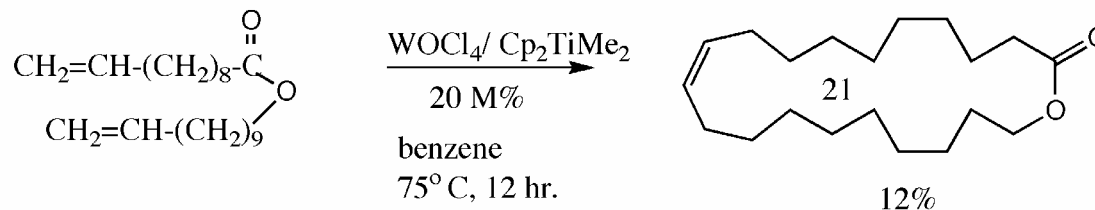
# Carbon-Carbon Double Bond Forming Reactions



# History of Ring Closing Metathesis



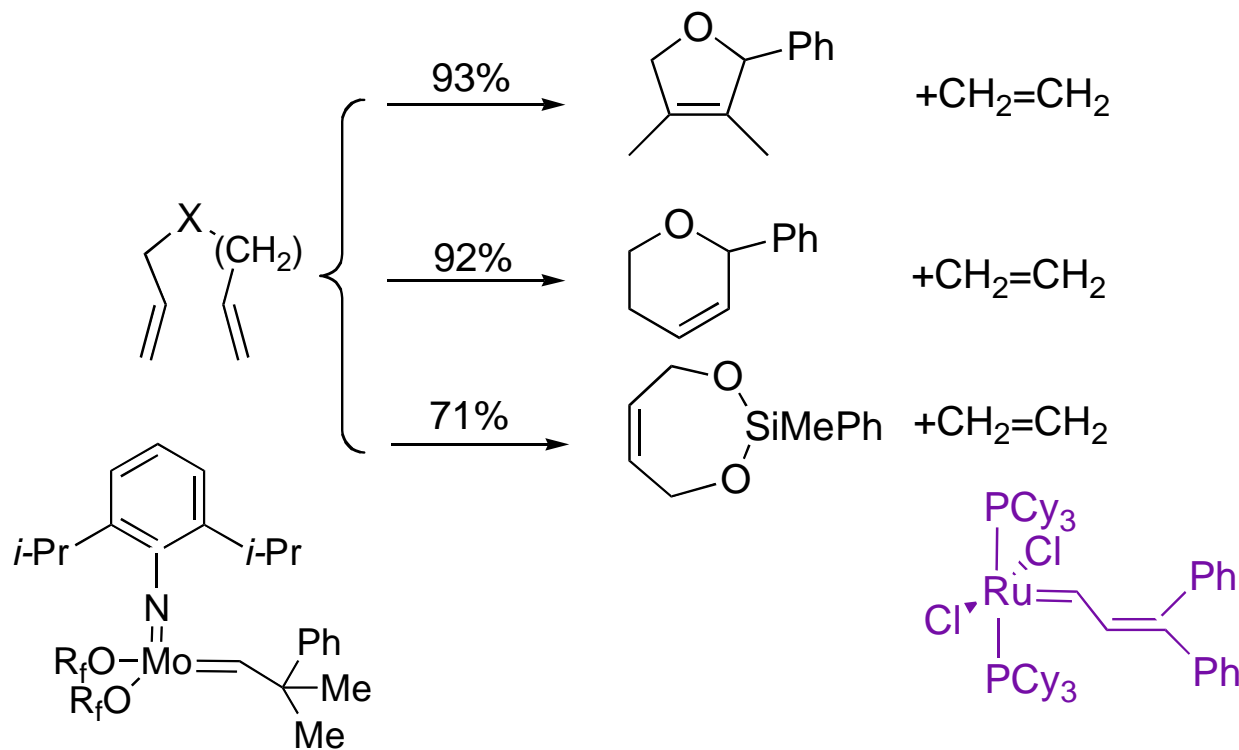
Didier Villemin, *Tetrahedron Letters*, **1980**, 1715



J. Tsuji and S Hashiguchi, *Tetrahedron Letters*, **1980**, 2955

**"In order to exploit the metathesis reaction as a truly useful synthetic methodology, it is essential to discover a new catalyst system which can tolerate the presence of functional groups in olefin molecules"- J. Tsuji**

# Ring Closing Metathesis with Well Defined Catalysts

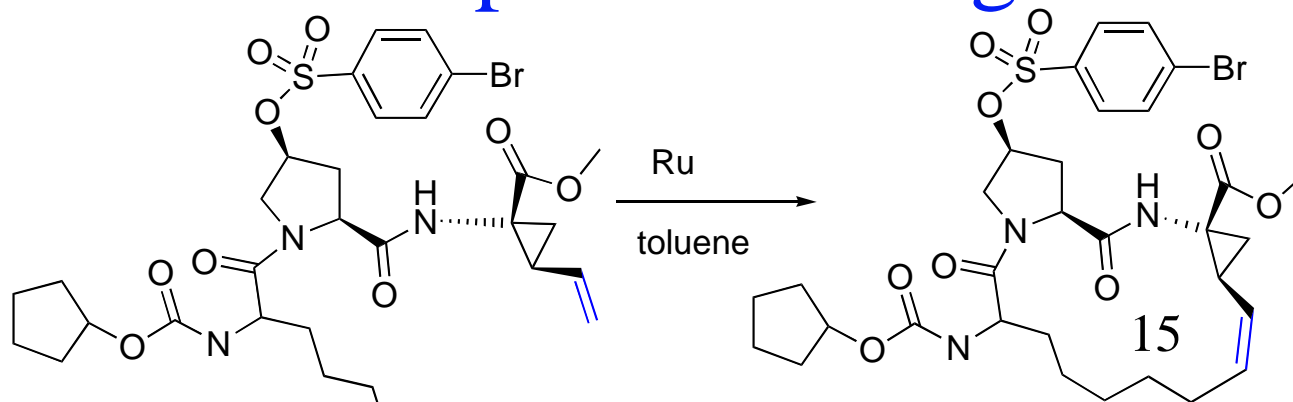


G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, **1992**, *114*, 5426-5427. *J. Am. Chem. Soc.* **1992**, *114* (18), 7324-7325. , *J. Am. Chem. Soc.*, **1993**, *115*, 3800-3801

G. C. Fu, S. T. Nguyen, and R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856-9857

# Pharmaceutical Applications

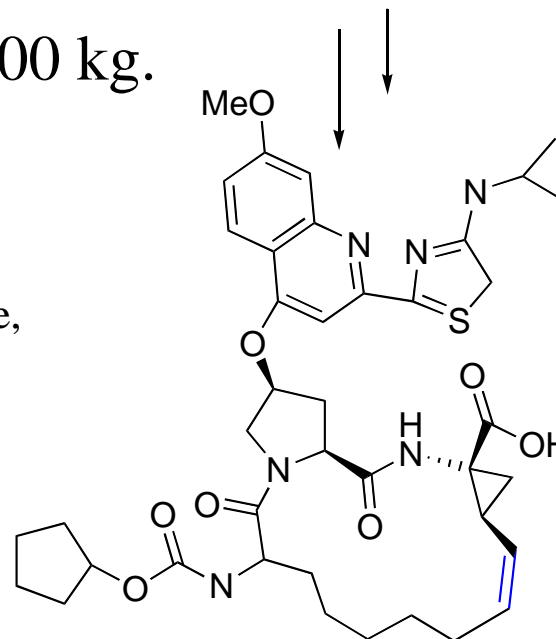
# Boehringer Ingelheim Hepatitis C Drugs



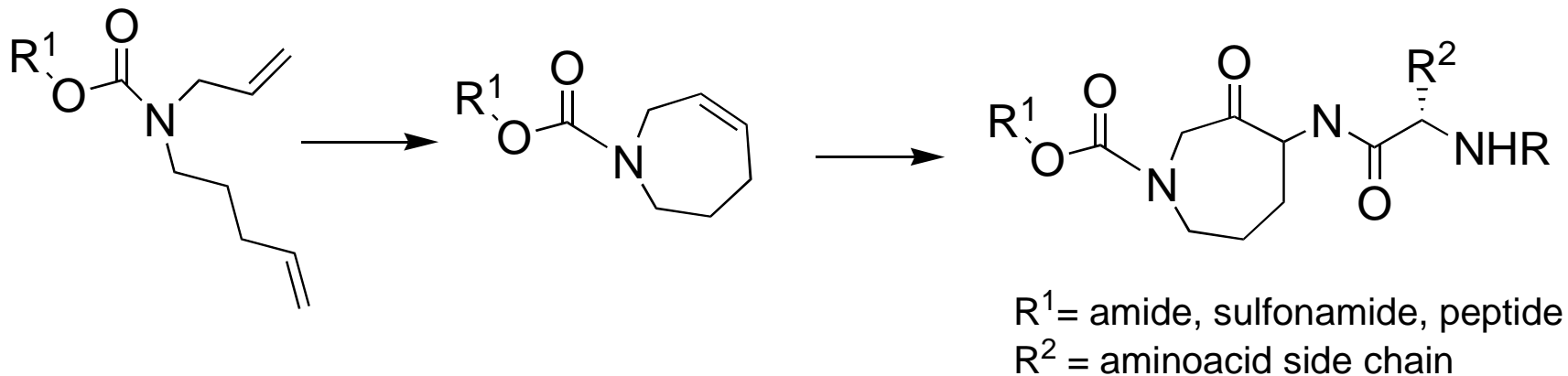
HCV Serine Protease Inhibitor  
Boehringer Ingelheim's BILN 2061  
Phase II Clinical Trials in US and Europe

400 kg.

T. Nicola, M. Brenner, K. Donsbach, and P. Kreye,  
*Organic Process and Development*, **2005**, 27.

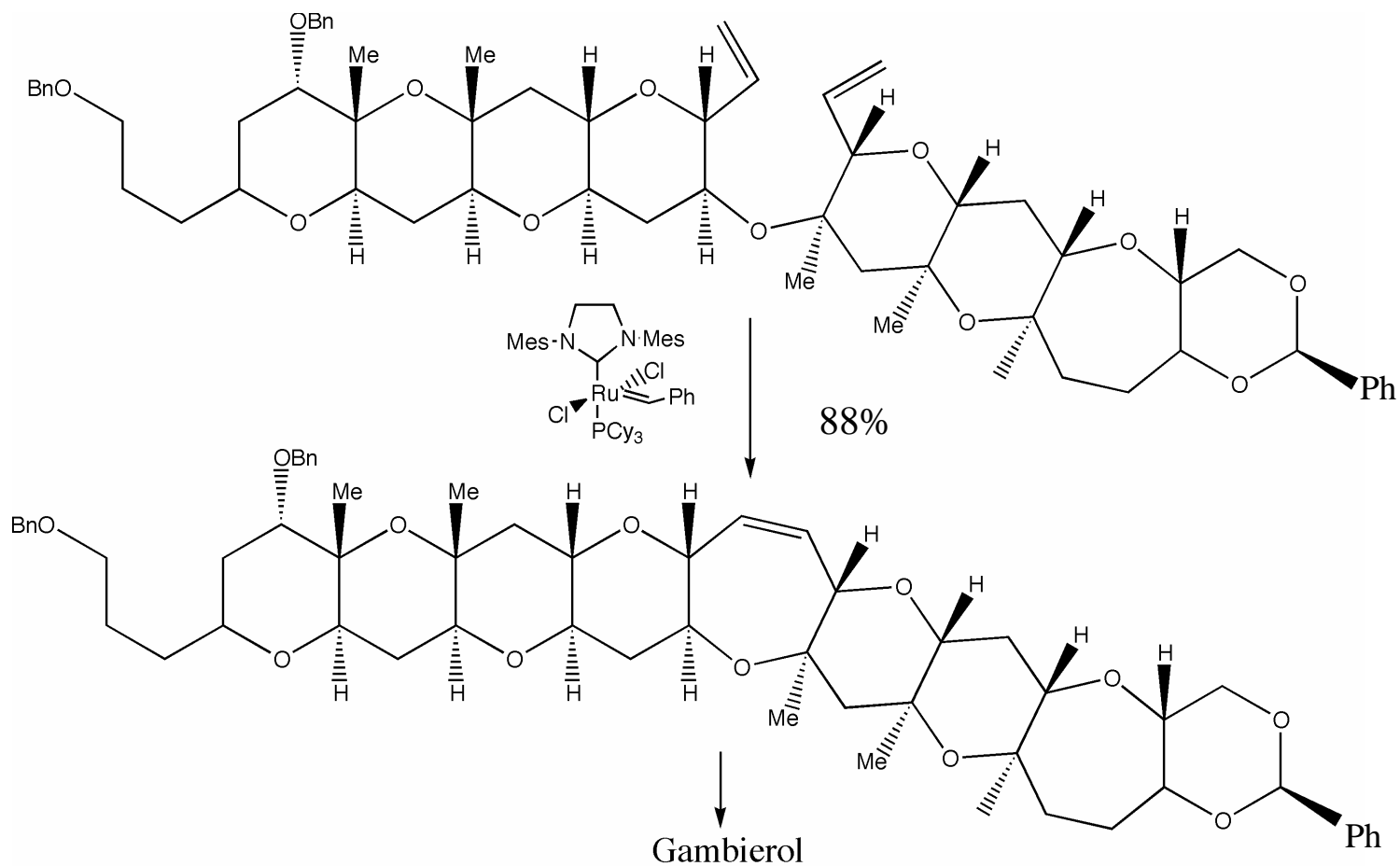


# GSK Osteoporosis Drug

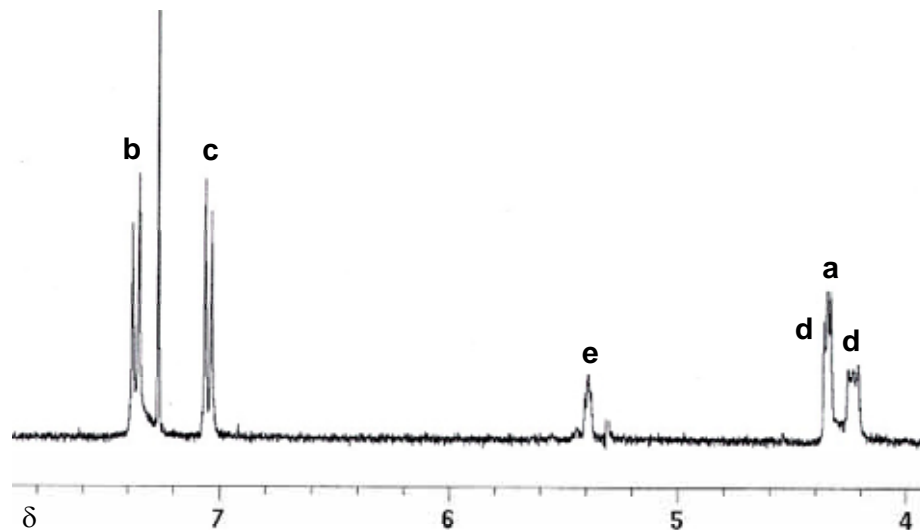
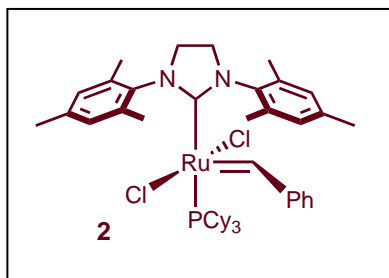
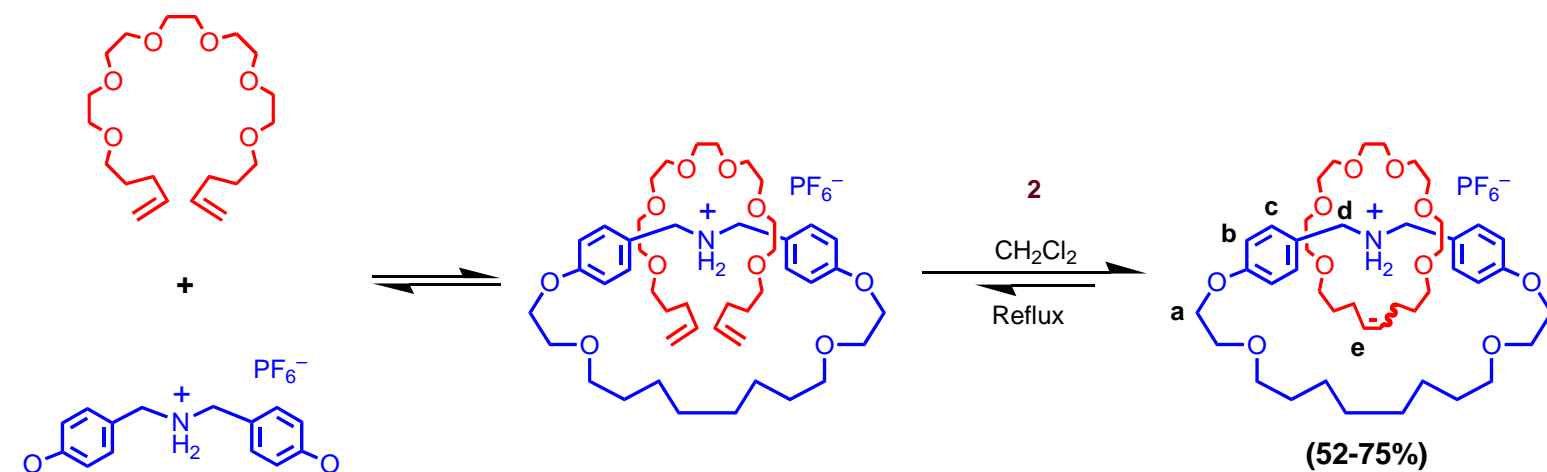


Protease Inhibitor of cathepsin K

# Synthesis of a Large Natural Product

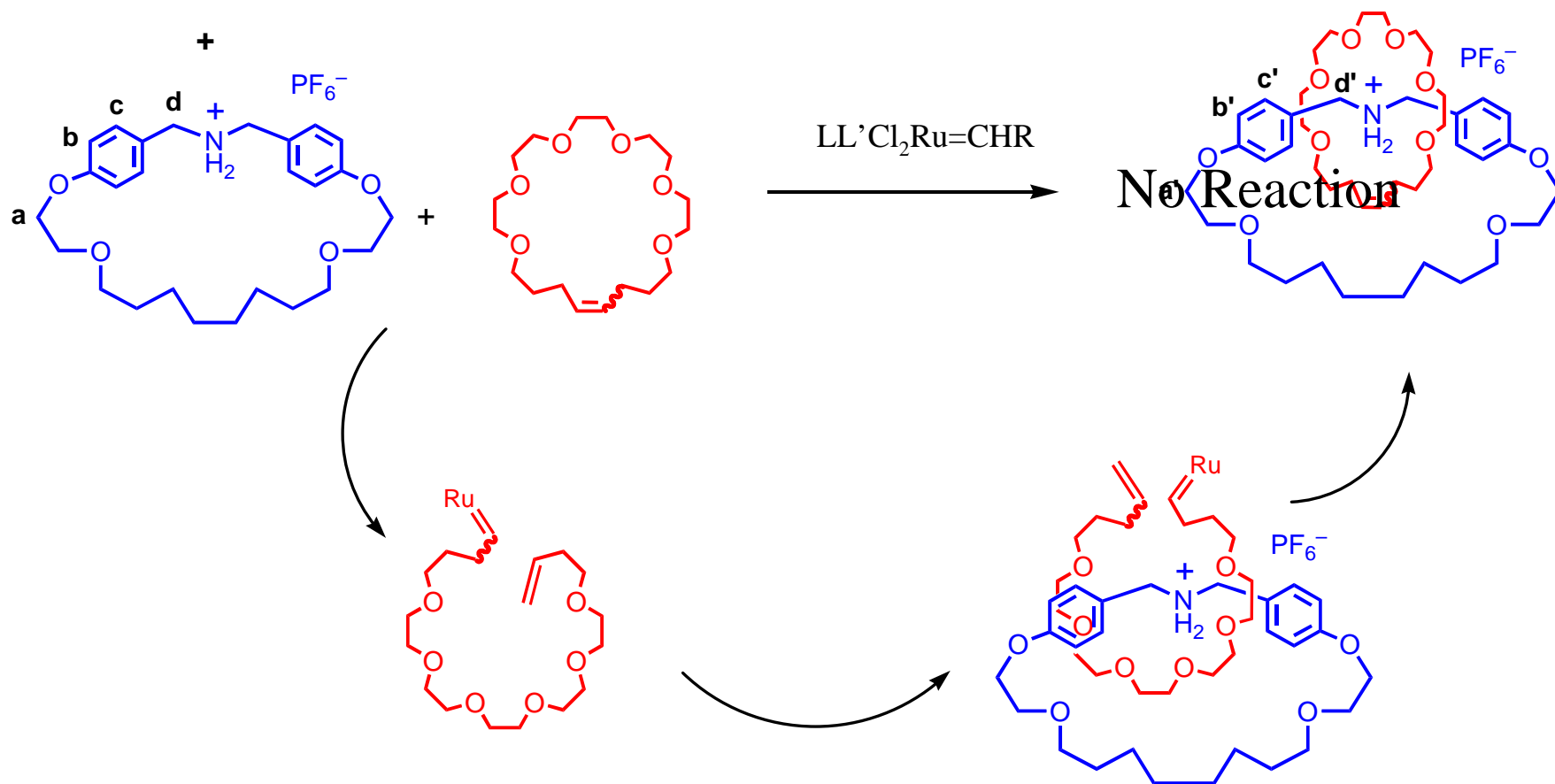


# Catenane Formation

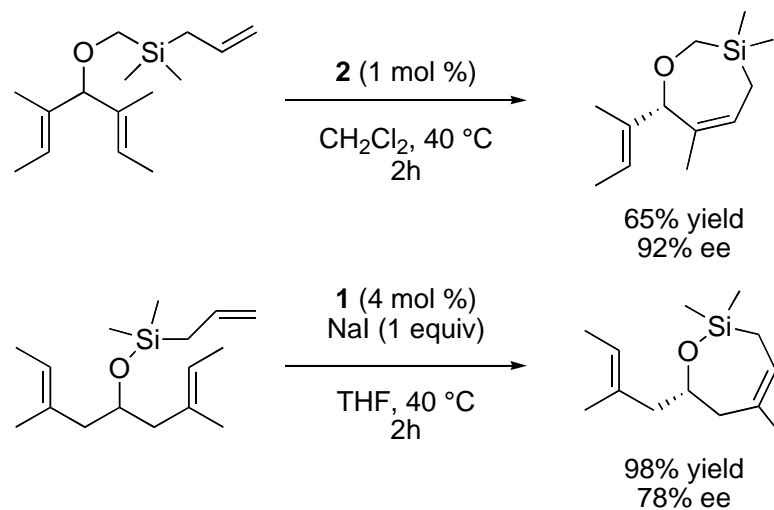
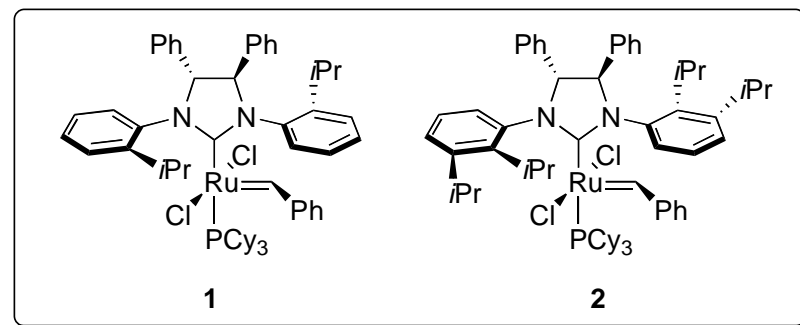
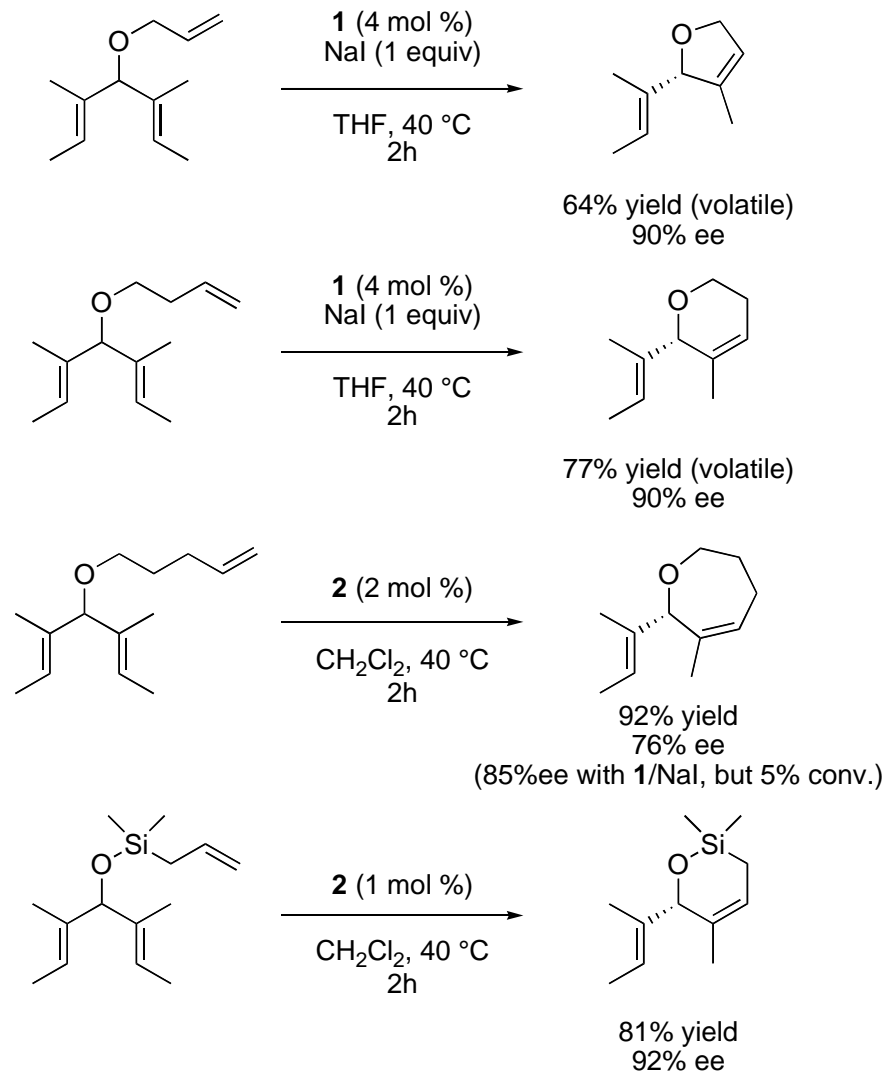




# Magic Rings



# Asymmetric Ring-Closing Metathesis



- Isolated yields
- 1 equiv. NaI relative to substrate; 25 equiv. relative to catalyst

# Green Chemistry

- Starting material
  - Renewable
  - Simple structures
- Processing
  - Few/no by products
  - No/little solvents (Water)
  - Low energy input
- Products
  - Replace polluting materials
  - Replace petroleum based material

# **A Codevelopment Program for the Conversion of Seed Oils to Value added Chemical**

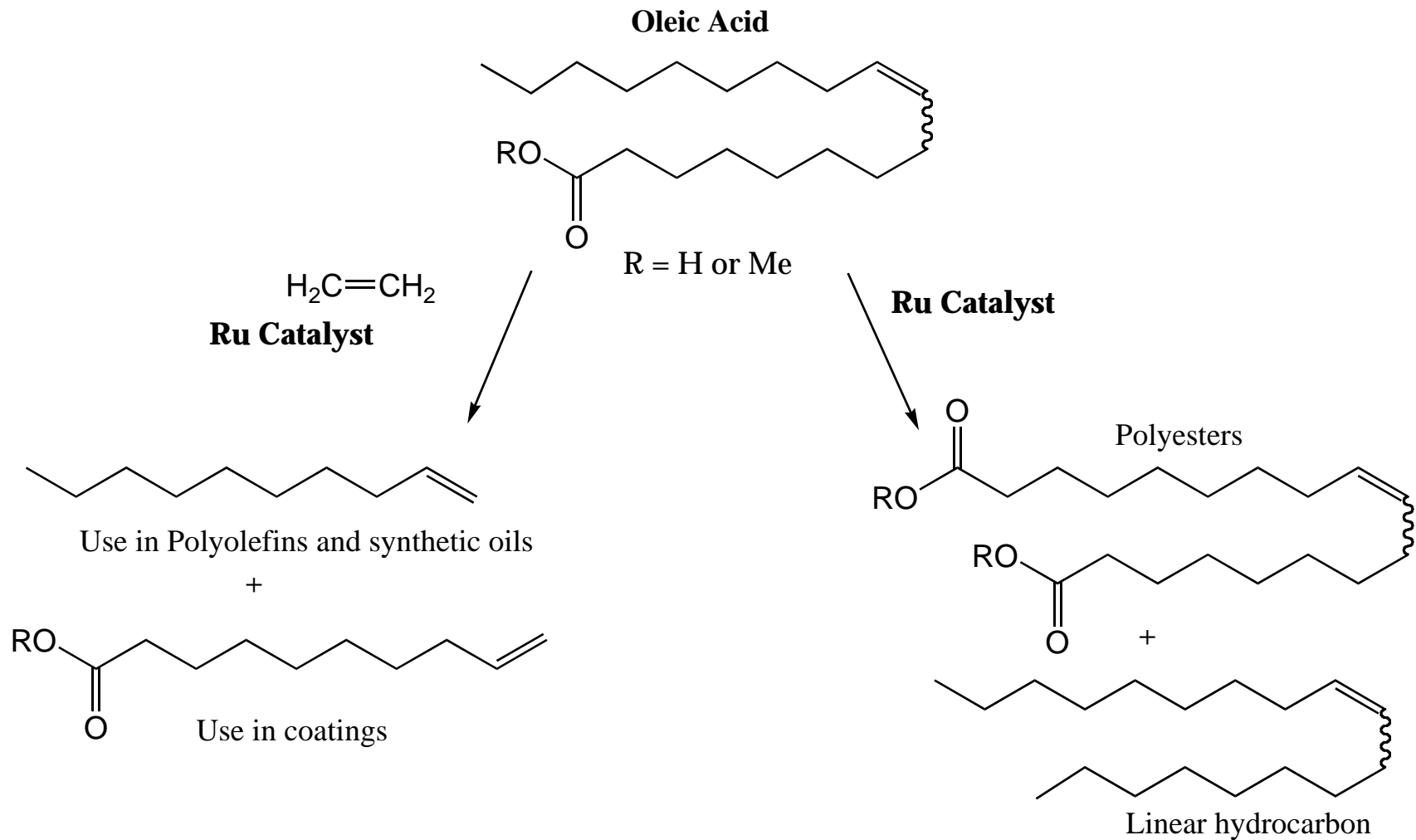
**Cargill- Materia- Caltech-DOE**

**Replace petroleum based products  
with those from renewable resources**

**Seed oils (corn and soy beans) are highly unsaturated (many double bonds)  
and  
can be modified by Olefin Metathesis  
to  
value added functional molecules**

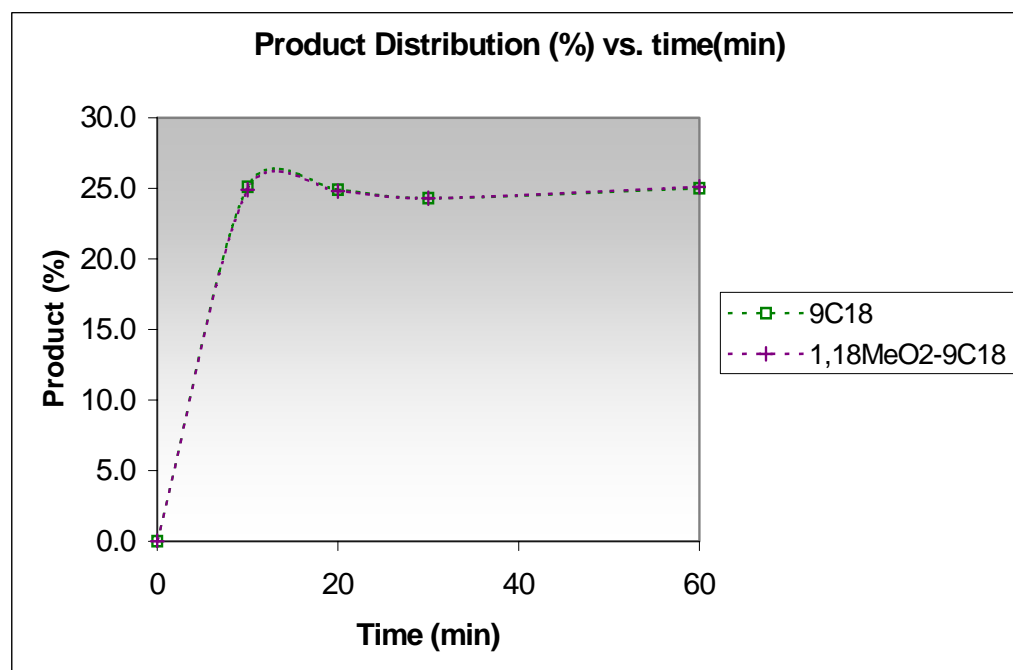
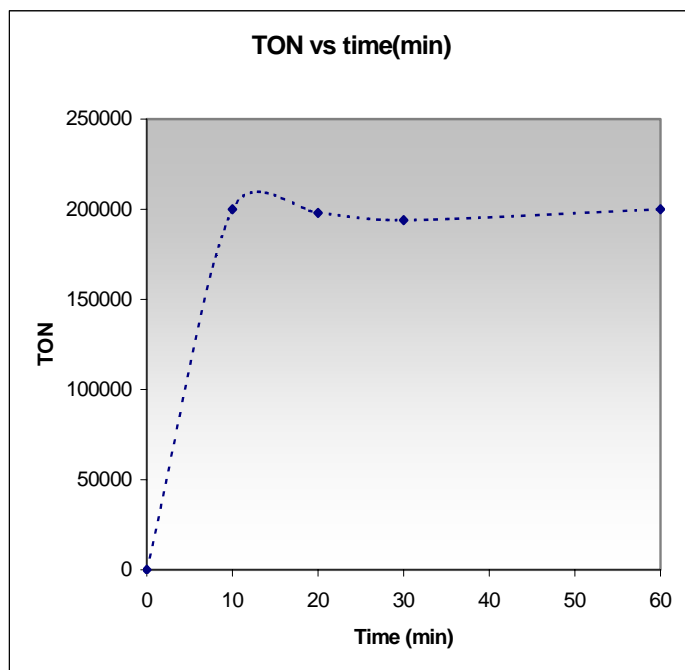
Cargill anticipates that it will have commercial sales in 2006 of several million pounds of a proprietary Ruthenium-metathesis based product derived from a renewable resource that will replace a petroleum-based material.

# Oleic Acid to Value Added Chemicals



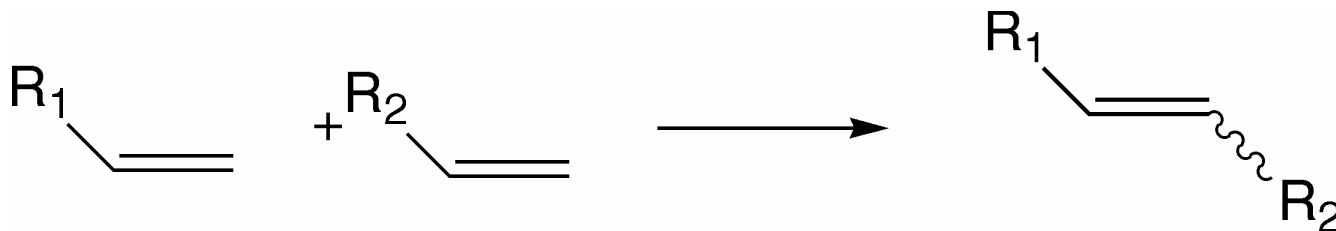
## Self-Metathesis of MO: C627 (5 ppm) at 40 °C

Sample #	Time (min)	MO (%)	9C <sub>18</sub> (%)	1,18MeO <sub>2</sub> -9C <sub>18</sub> (%)	Impurities (%)	SM (%)	TON
0	0	100.0	0.0	0.0	0.0	0	0
067-007-1-10	10	49.9	25.1	24.9	0.1	100	200000
067-007-1-20	20	50.3	24.9	24.8	0.0	99	198000
067-007-1-30	30	51.4	24.3	24.3	0.0	97	194000
067-007-1-60	60	49.9	25.0	25.1	0.0	100	200000



**TON = 200,000; TOF = 1,200,000 h<sup>-1</sup>; extremely low impurity formation**

# Statistical Distribution of CM Products



$R_1 : R_2$       CM yield

1 : 1      50%

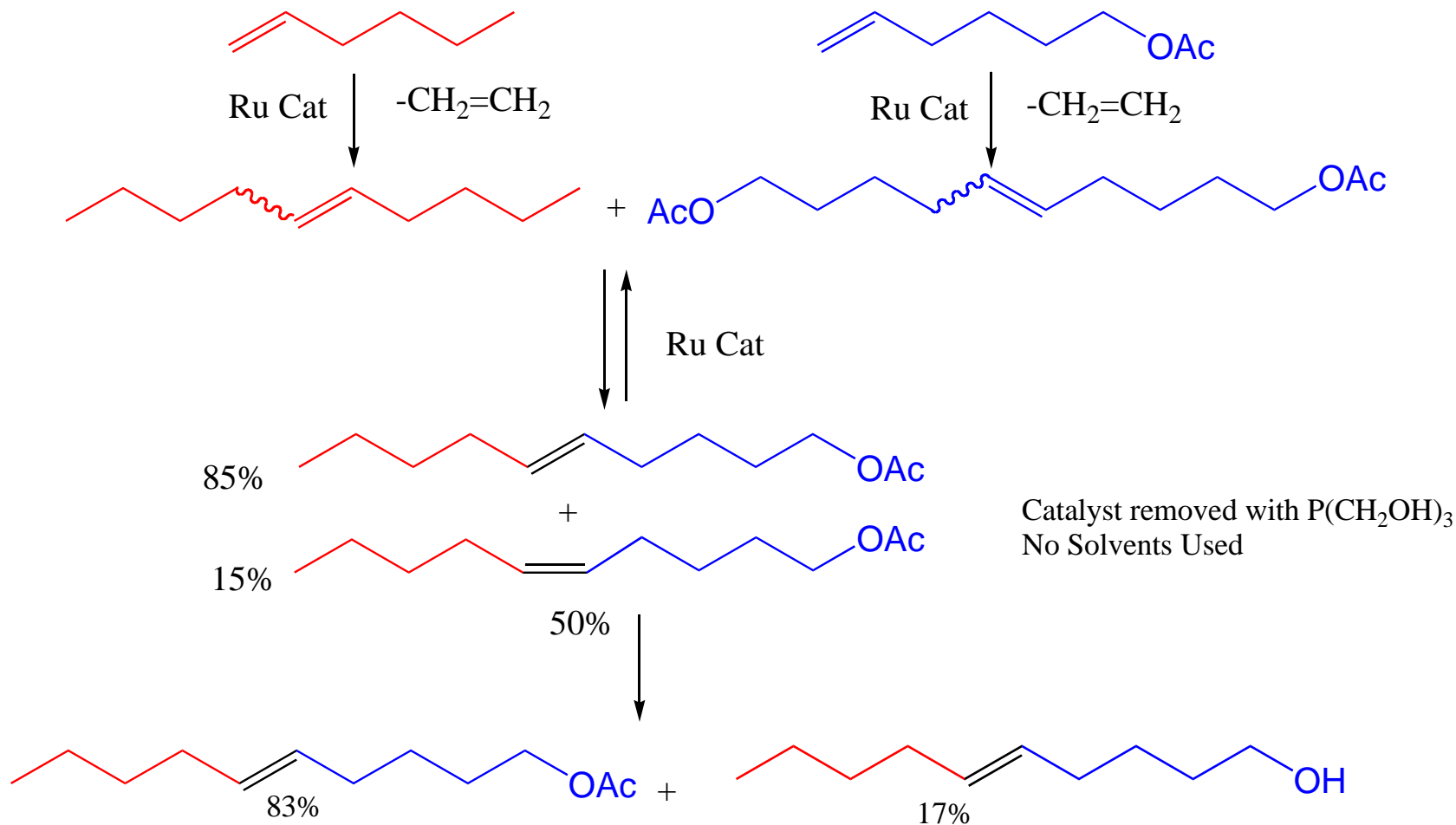
2 : 1      66%

4 : 1      80%

10 : 1      91%

20 : 1      95%

# Pheromone by Cross Metathesis

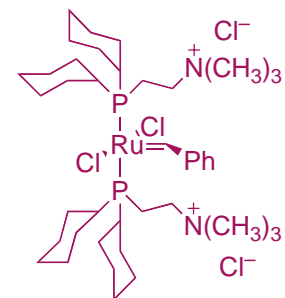
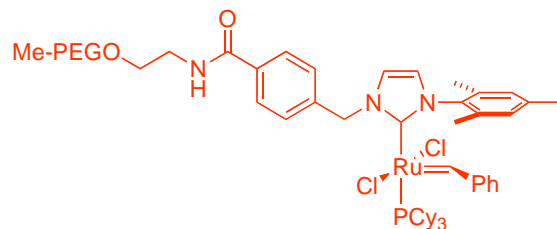
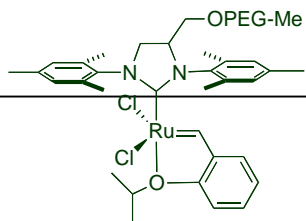
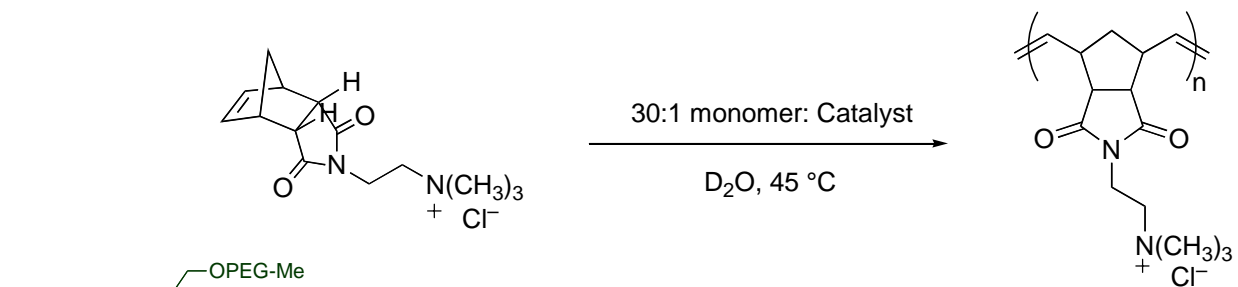


PHEROMONE for Peach Twig Borer  
Used in Mating Disruption

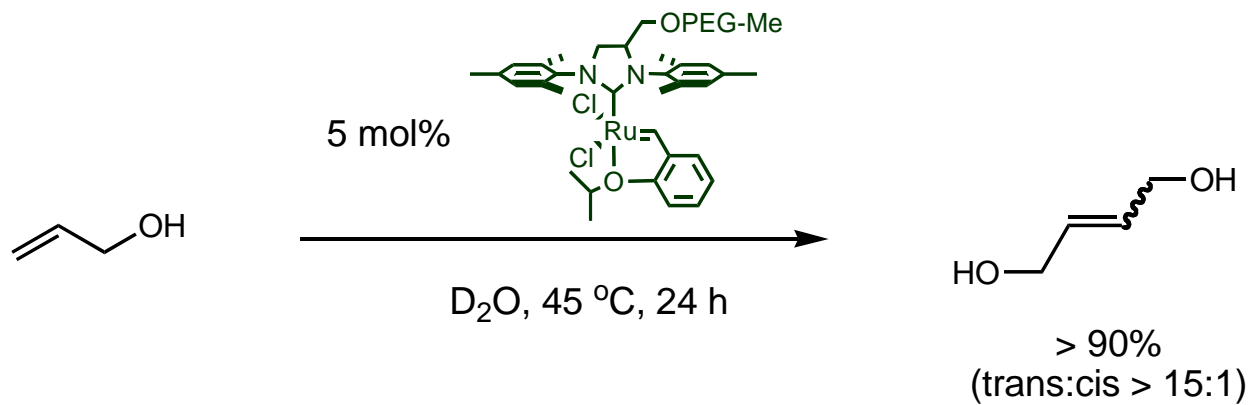
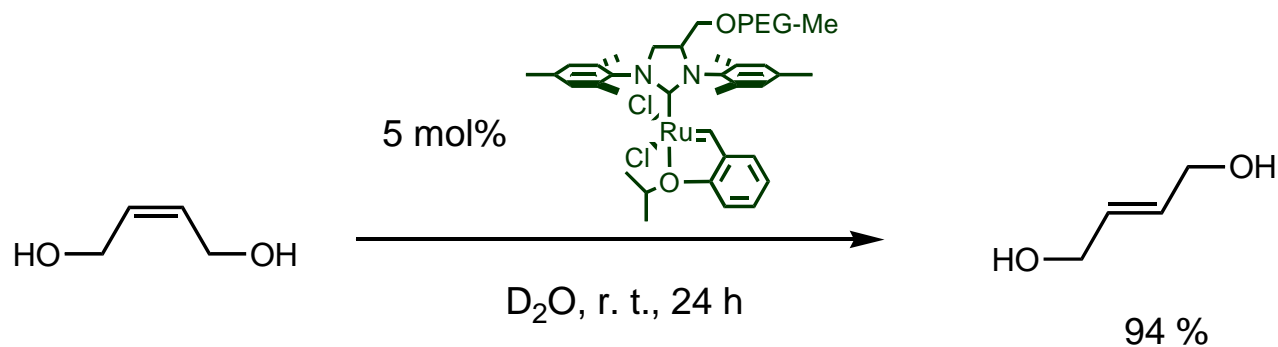
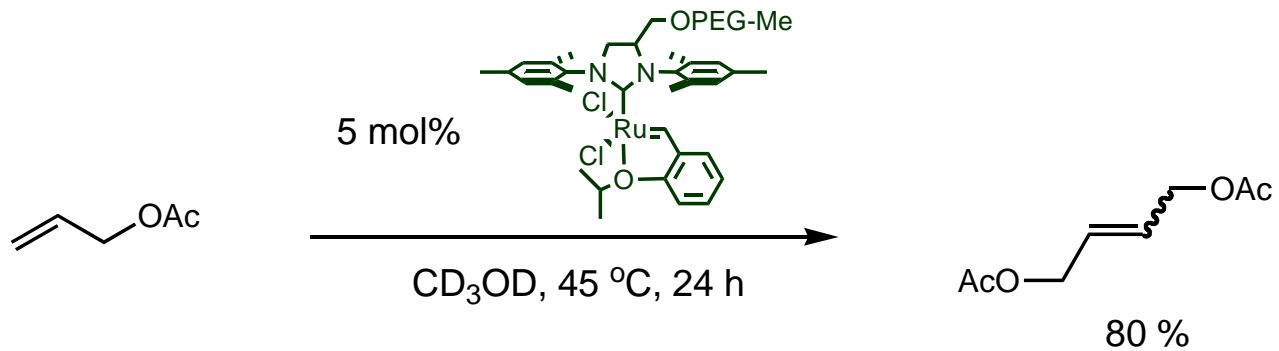


# Water as a Solvent

# ROMP of Water-Soluble Endo-Monomer



# Cross Metathesis

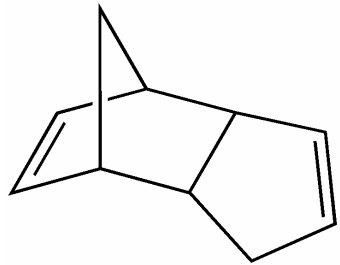


# Polymer Synthesis

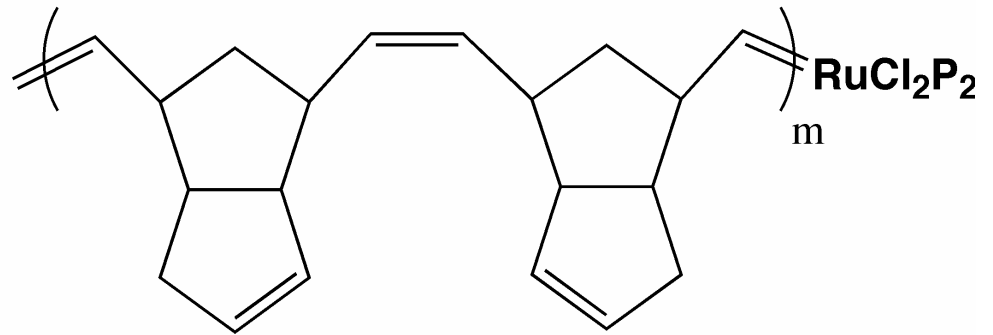
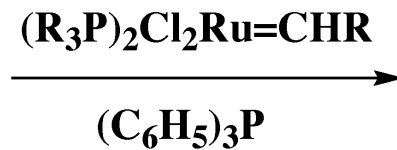
Mechanical Properties

Chemical Function

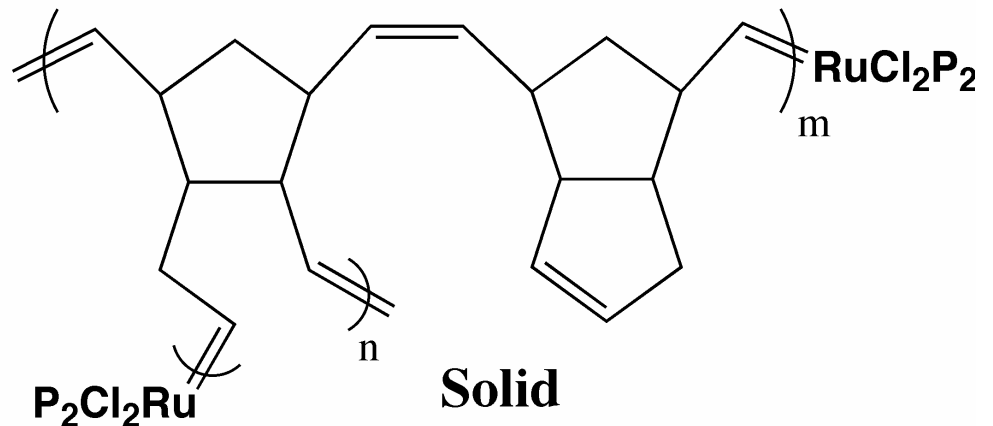
# Dicyclopentadiene-Thermoset Polymer



**Liquid**



Cross-link



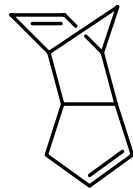
$T_g > 120^\circ C$  E-modulus > 2000 MPa

Impact > 10 psi

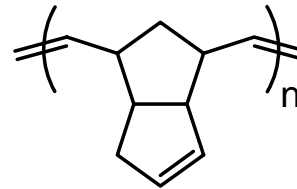
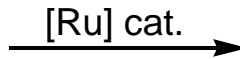
# PolyDCPD-9mm Ballistic Protection



# Products Made With DCPD ROMP



DCPD



poly(DCPD)



Consumer products



Truck Parts



Sports Equipment

[www.plastictechnology.com](http://www.plastictechnology.com)  
[baseball.eastonsports.com](http://baseball.eastonsports.com)

# Acknowledgements

- All my Professors and others who have provided inspiration on my journey from the American equivalent of Åmål.
- The over 200 co-workers who have contributed to my research.
- Financial support of NSF, NIH, DoD, Matera ---
- Helen and the gang- Barney, Brendan and Katy.