

Olefin Metathesis Catalysts for the Synthesis of Molecules and Materials

December 8, 2005

Stockholm, Sweden

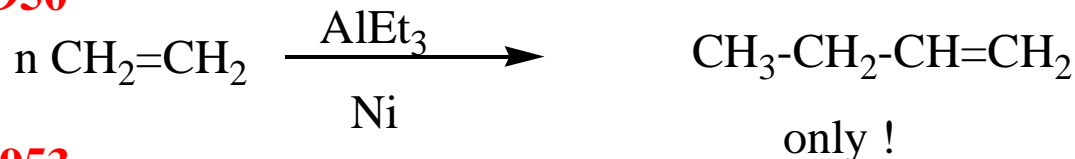
New Polyethylene

Ziegler --MPI in Mulheim

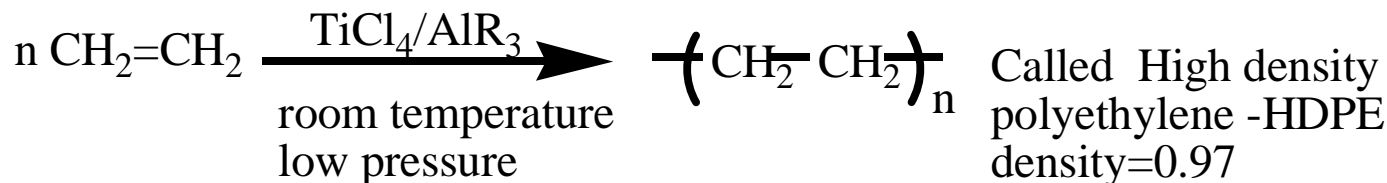
1940's- war years



1950⁺



1953



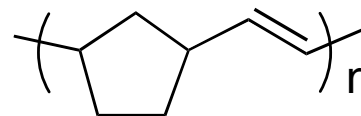
Crystalline - Milk bottles

K. Ziegler and G. Natta, Nobel Prize 1963

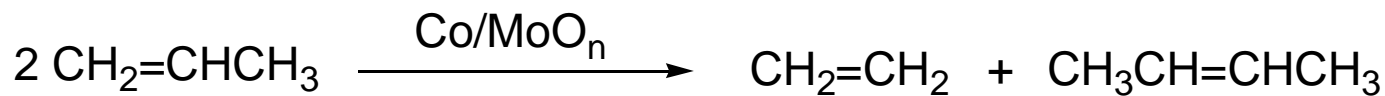
Discovery of a New Reaction



Polymer containing unsaturation-
unexpected for an addition polymer



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



Three carbons

Two carbons

Four carbons

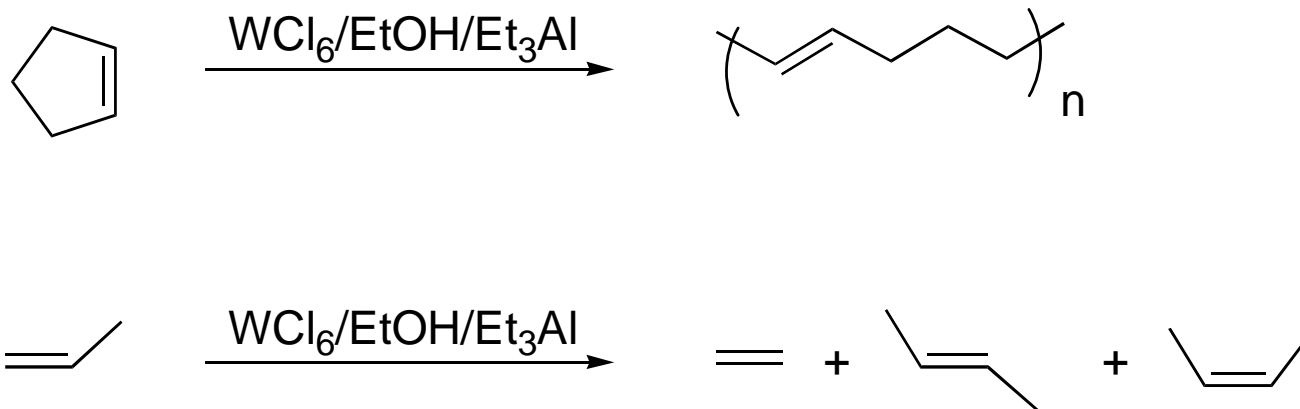
Heterogeneous Catalyst

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

Metathesis Discovery

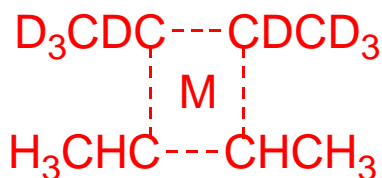
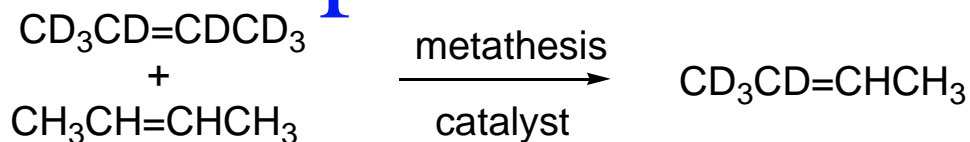


Natta, et. al. J. Polymer Sci., Polymer Lett. 1964, B2, 349

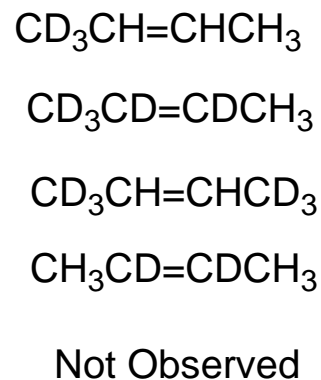


Calderon, Chen, Scott, Tetrahedron Letters, 1967, 3327

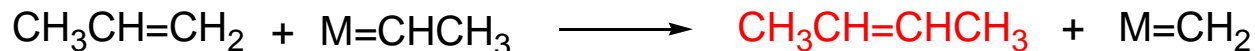
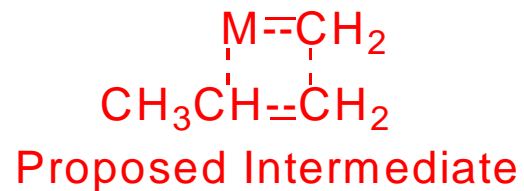
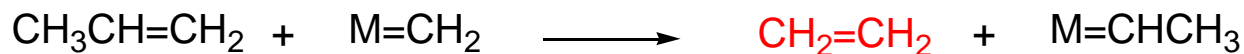
Proposed Mechanisms



Proposed intermediate

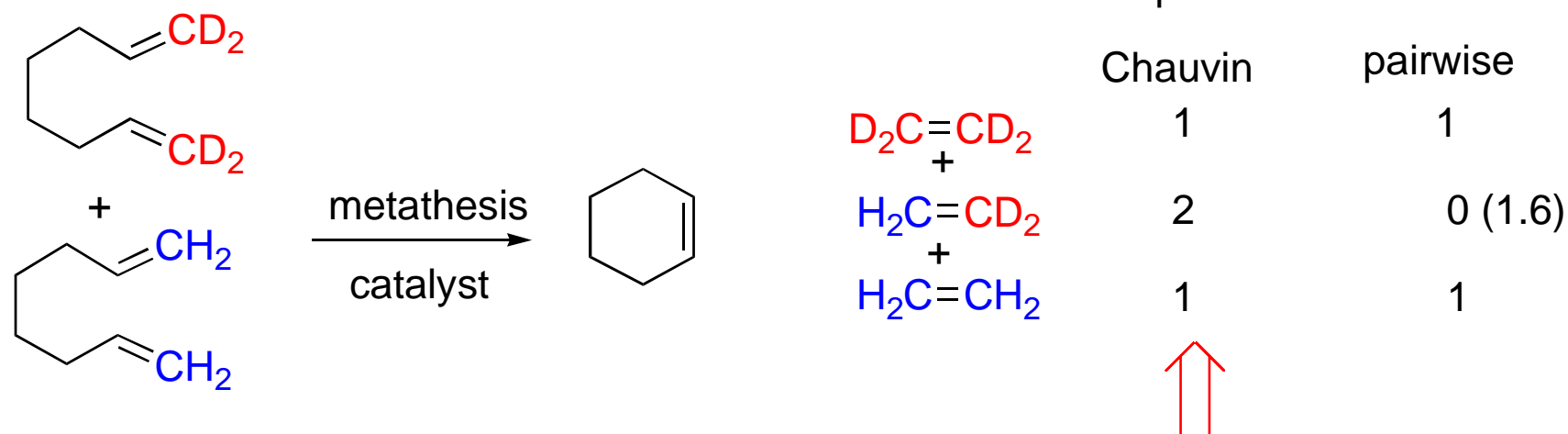
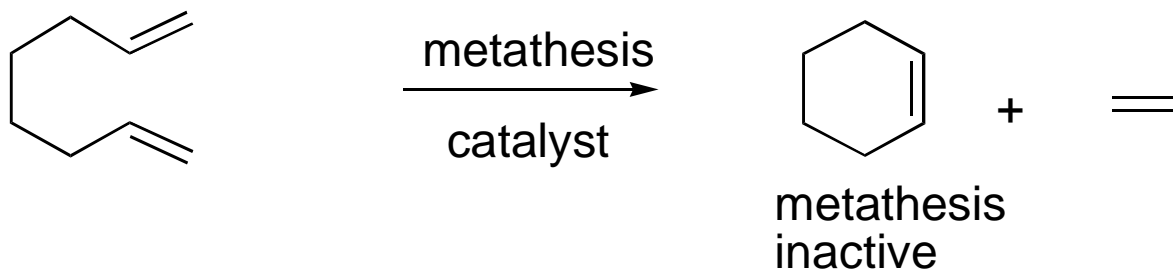


N. Calderon, E. A. Olfsead, J. P. Ward, W. A. Judy, K. W. Scott, *J. Am. Chem. Soc.*, **1968**, *90*, 4133



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

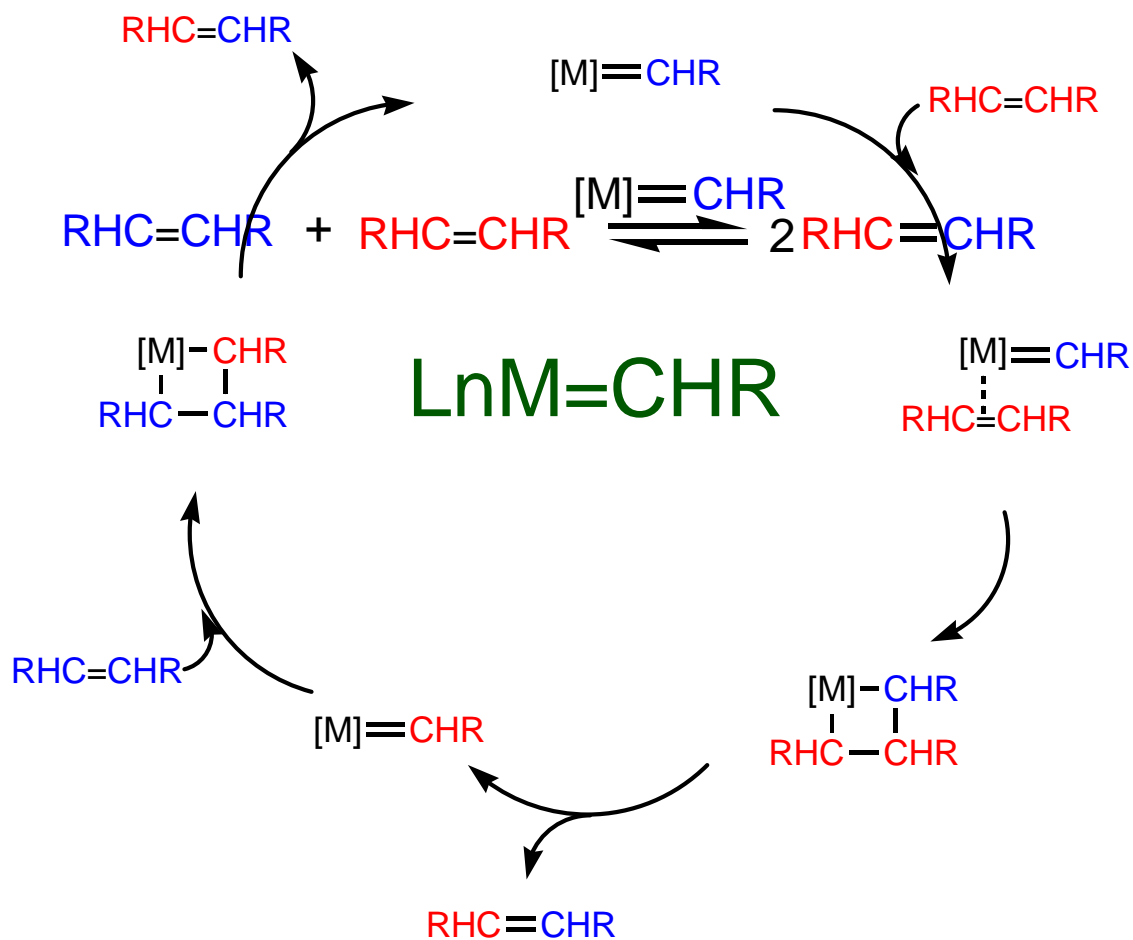
Mechanistic Study



OBSERVED

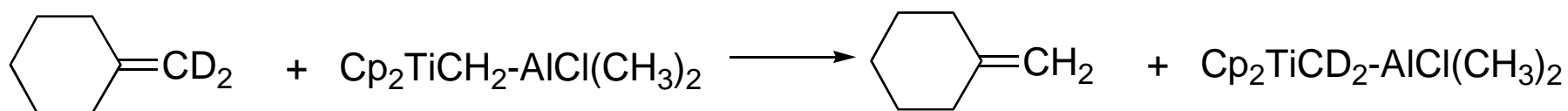
R. H. Grubbs, P. L. Burk and D. D. Carr, *J. Am. Chem. Soc.* **1975**, 97, 3265.
 T. J. Katz and R. Rothchild, *J. Am. Chem. Soc.* **1976**, 98, 2519.

Olefin Metathesis Mechanism



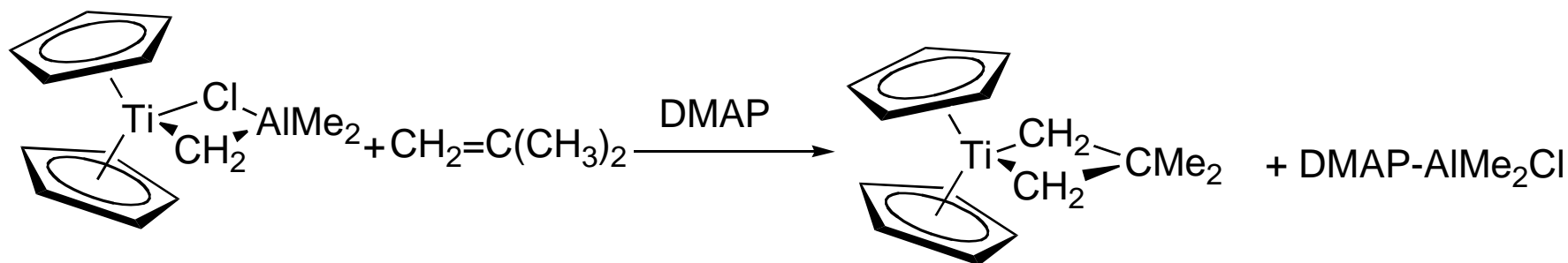
Carbene Catalysts

Demonstration of Exchange between Metal Methylene and an Olefin



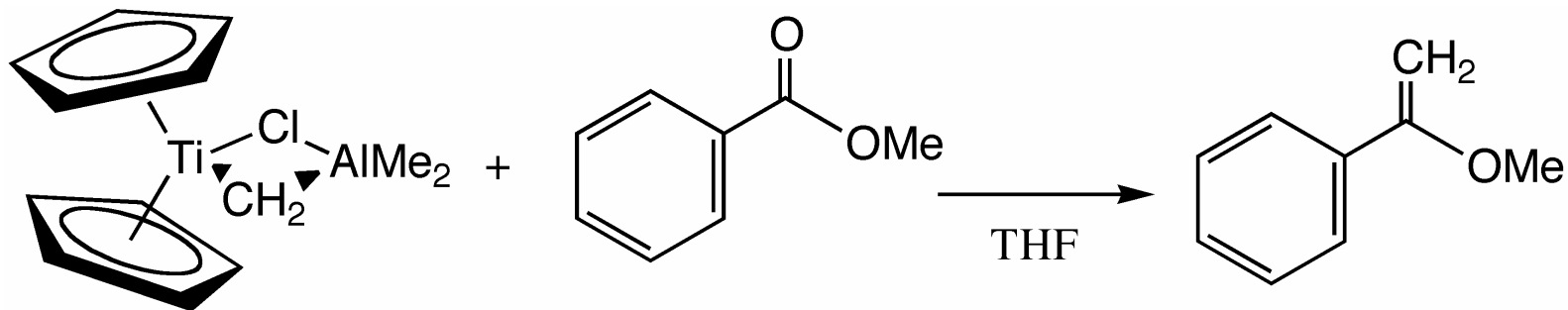
F.N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611

Isolation of Metallacycle in Active Metathesis System



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

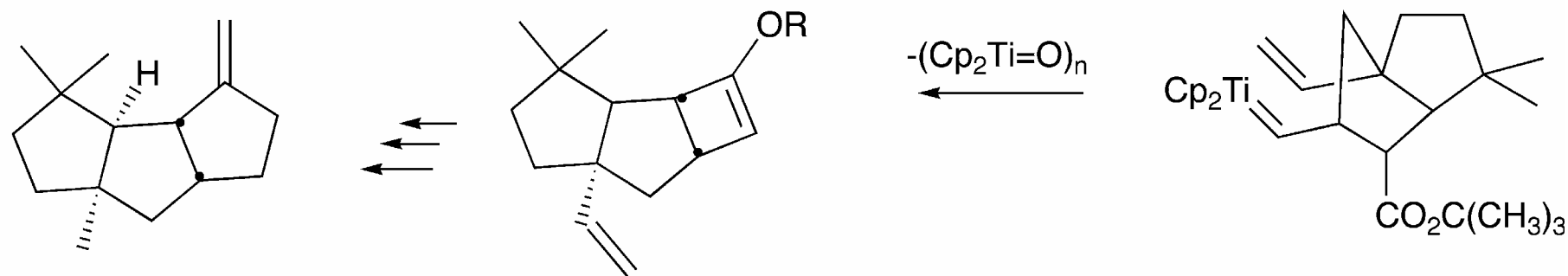
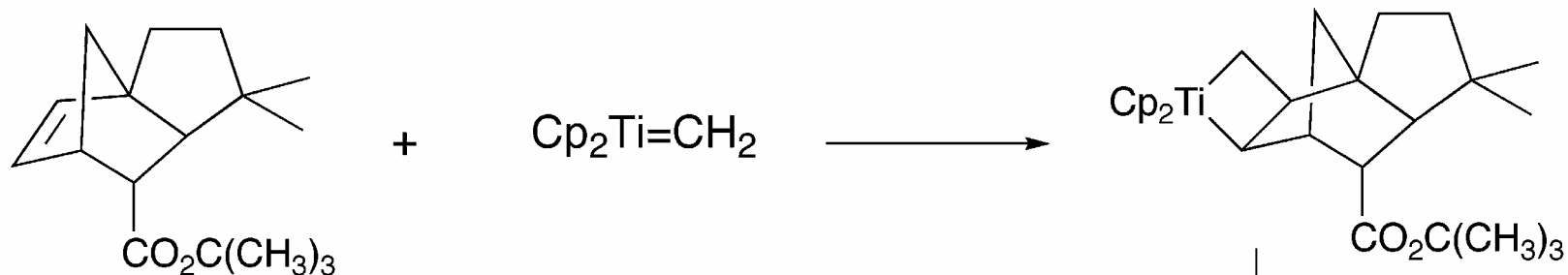
Tebbe Reagent



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

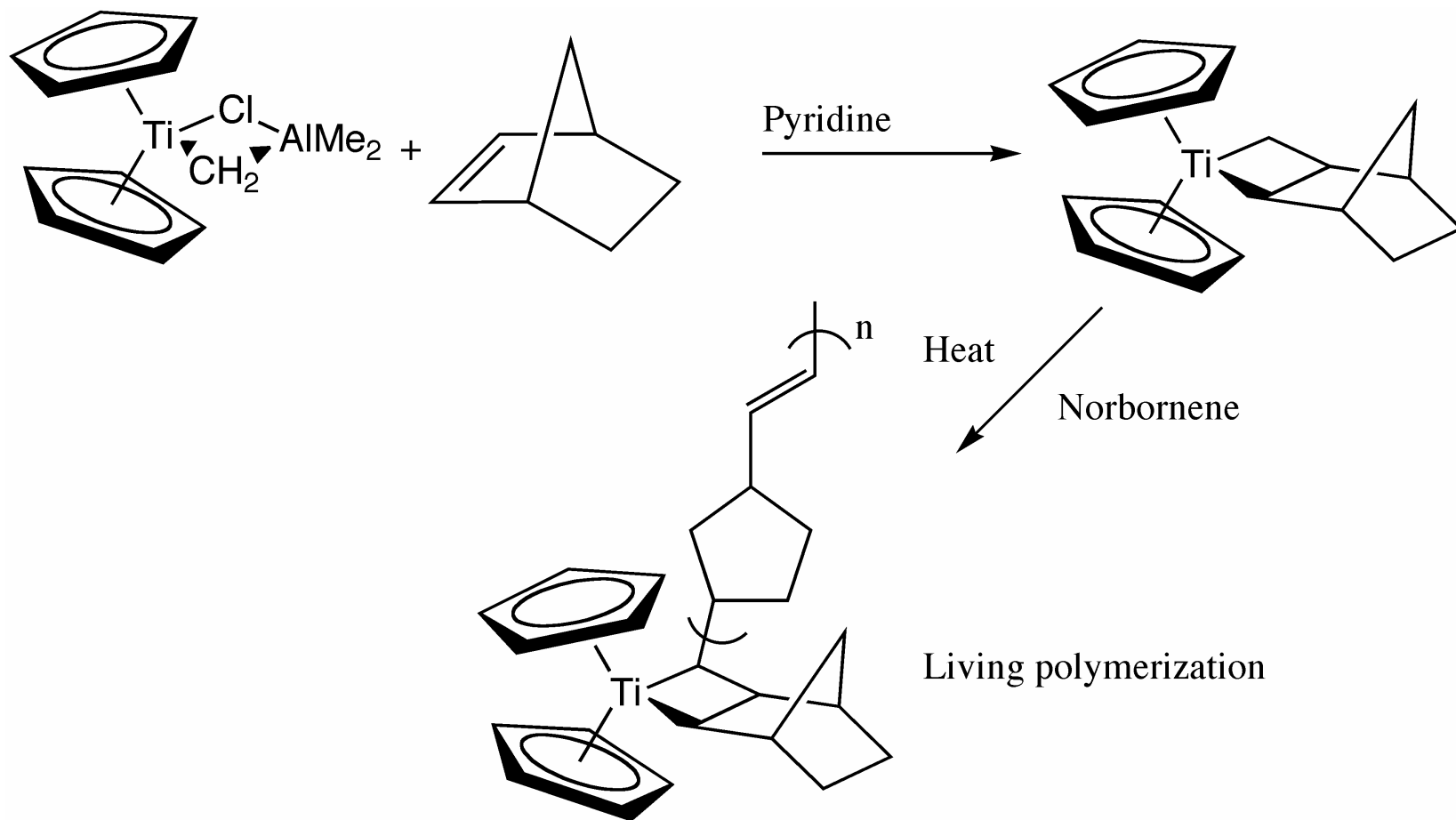
Metal Alkylidenes in Organic Synthesis

Tebbe Reagent in Synthesis

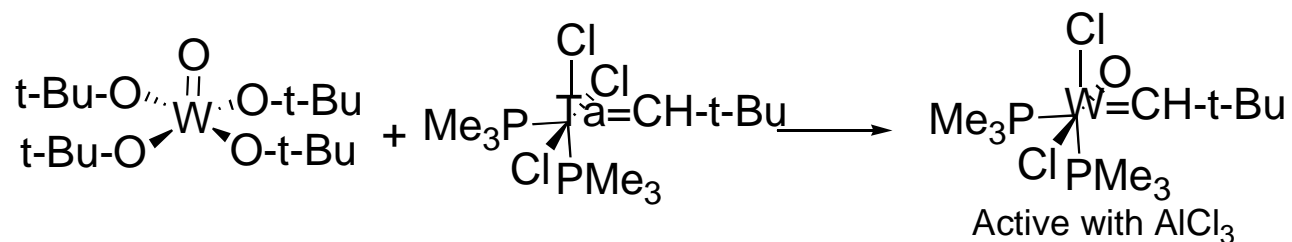


\triangle ^(9,12)-Capnellene

Living ROMP Polymers

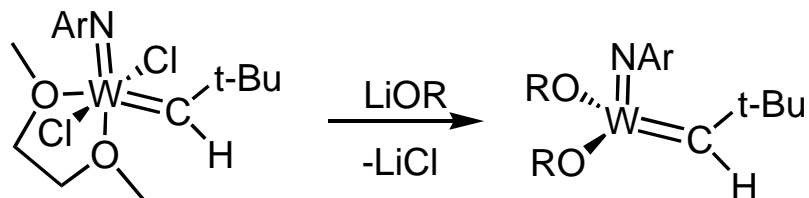


Schrock Alkylidenes



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



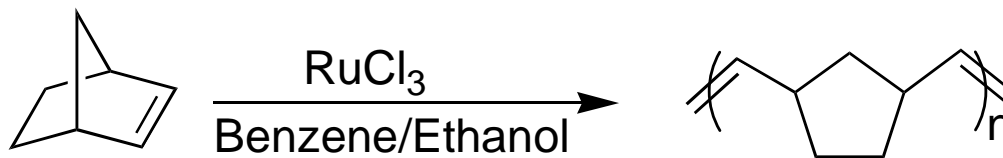
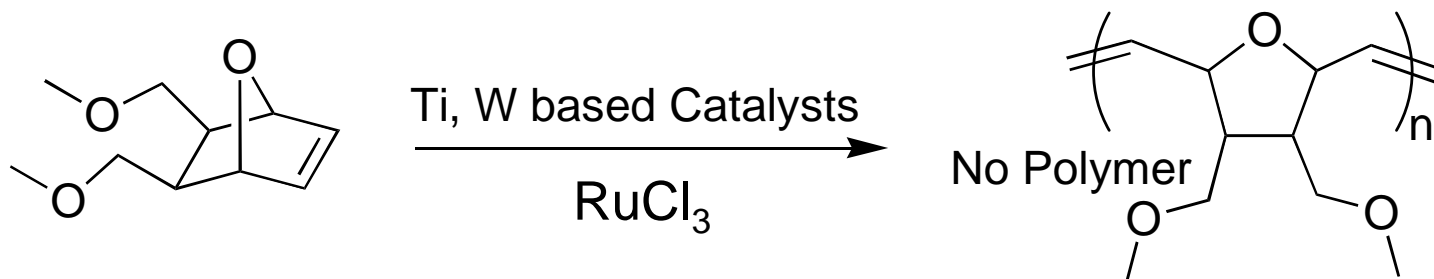
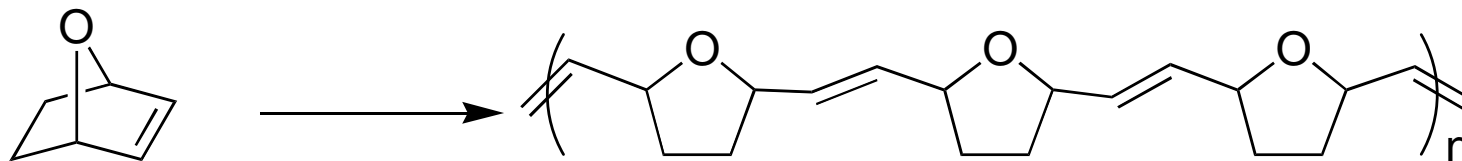
also Mo
Analog

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)

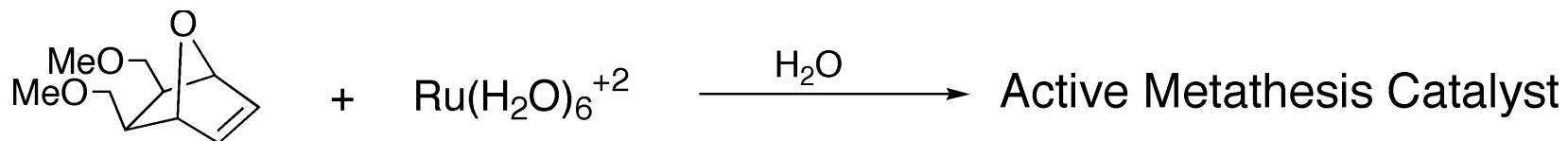
The Ruthenium Story

Synthesis of an Ionophore



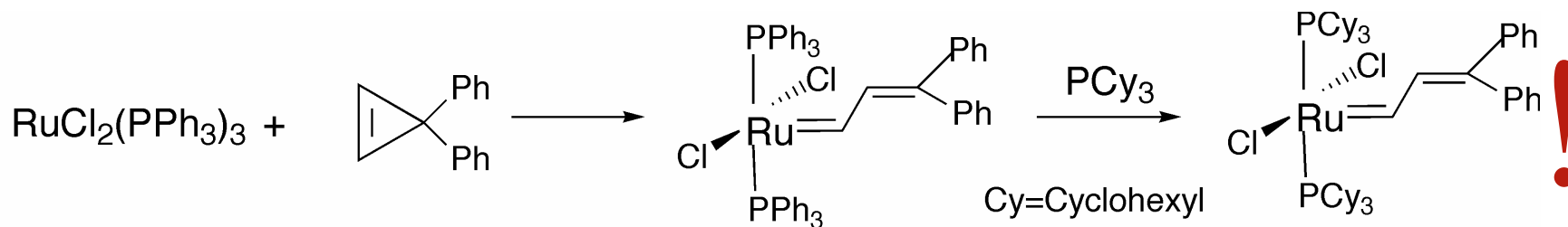
F. W. Michelotti, W. P. Keaveney, *J. Poly. Sci., Part A*, **1965**, 895

Ruthenium Catalyst Synthesis



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

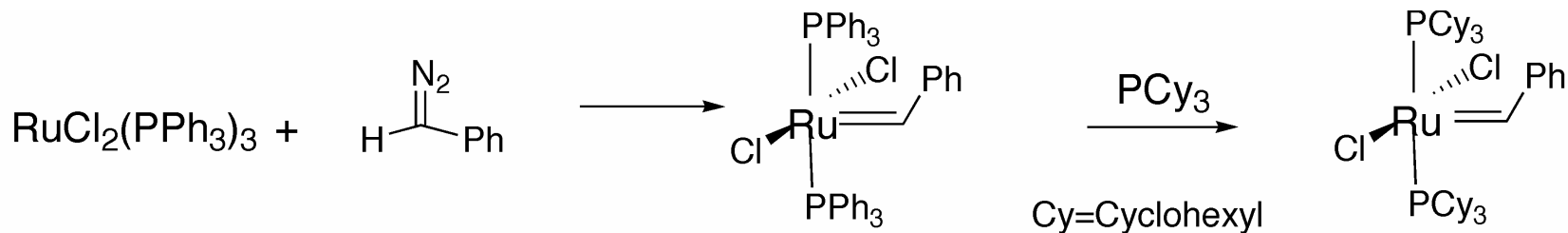
Ill defined, highly active, little initiation



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

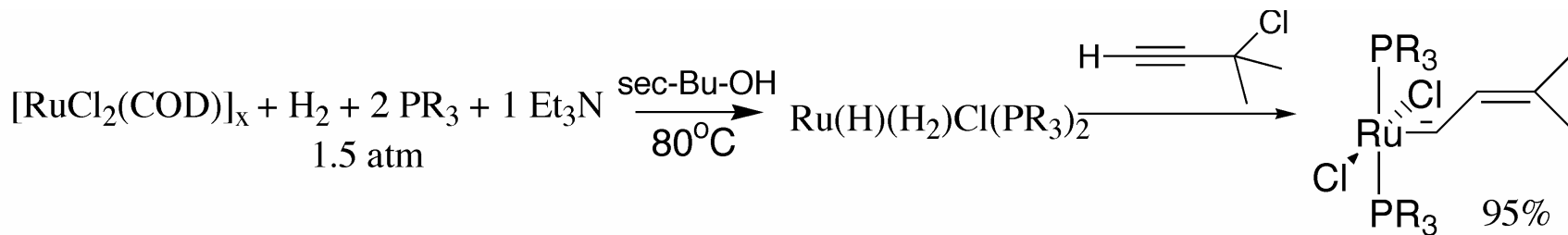
Well defined, good activity, 100mg/week

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	VIII	VIII	VIII	IB	IB	13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	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								

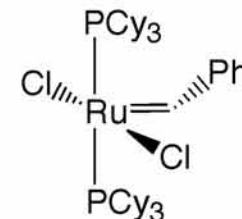
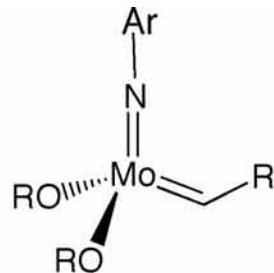
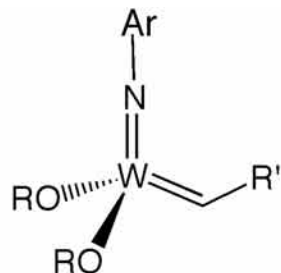
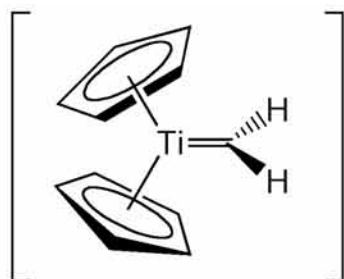
*Lanthinide Series

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

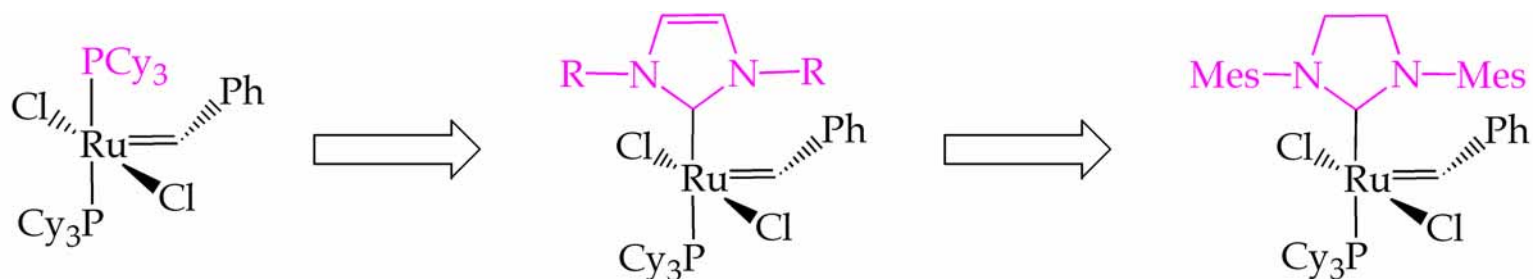
Esters, Amides

functional group tolerance

Activity

Increasing
order of
reactivity

Catalyst Developments at Caltech



And Nolan and Herrmann



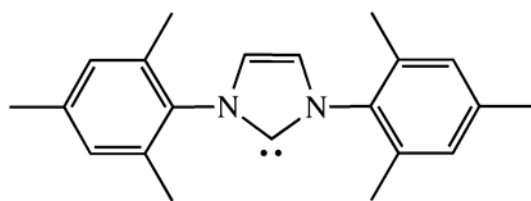
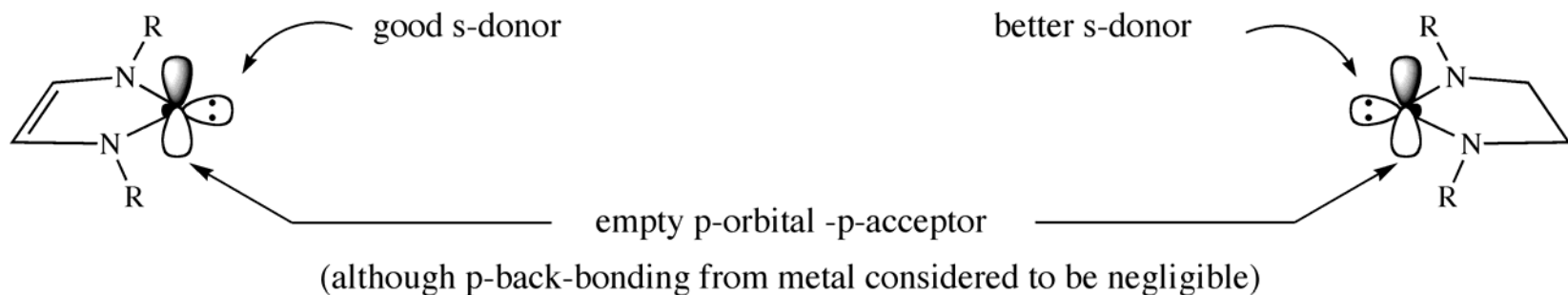
NHC catalysts are more active for RCM and ROMP (by 10^2 - 10^3)

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.

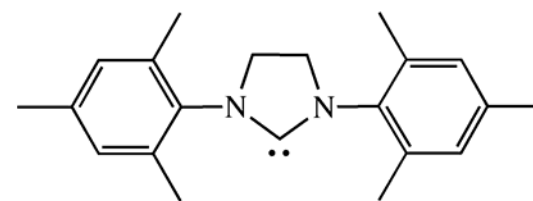
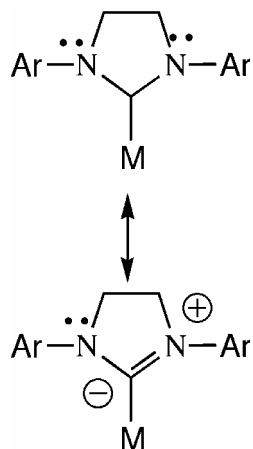
N-Heterocycle Carbene Ligands

Singlet carbenes (as in N-Heterocyclic Carbenes)



IMes

1,3-dimesitylimidazol-2-ylidene

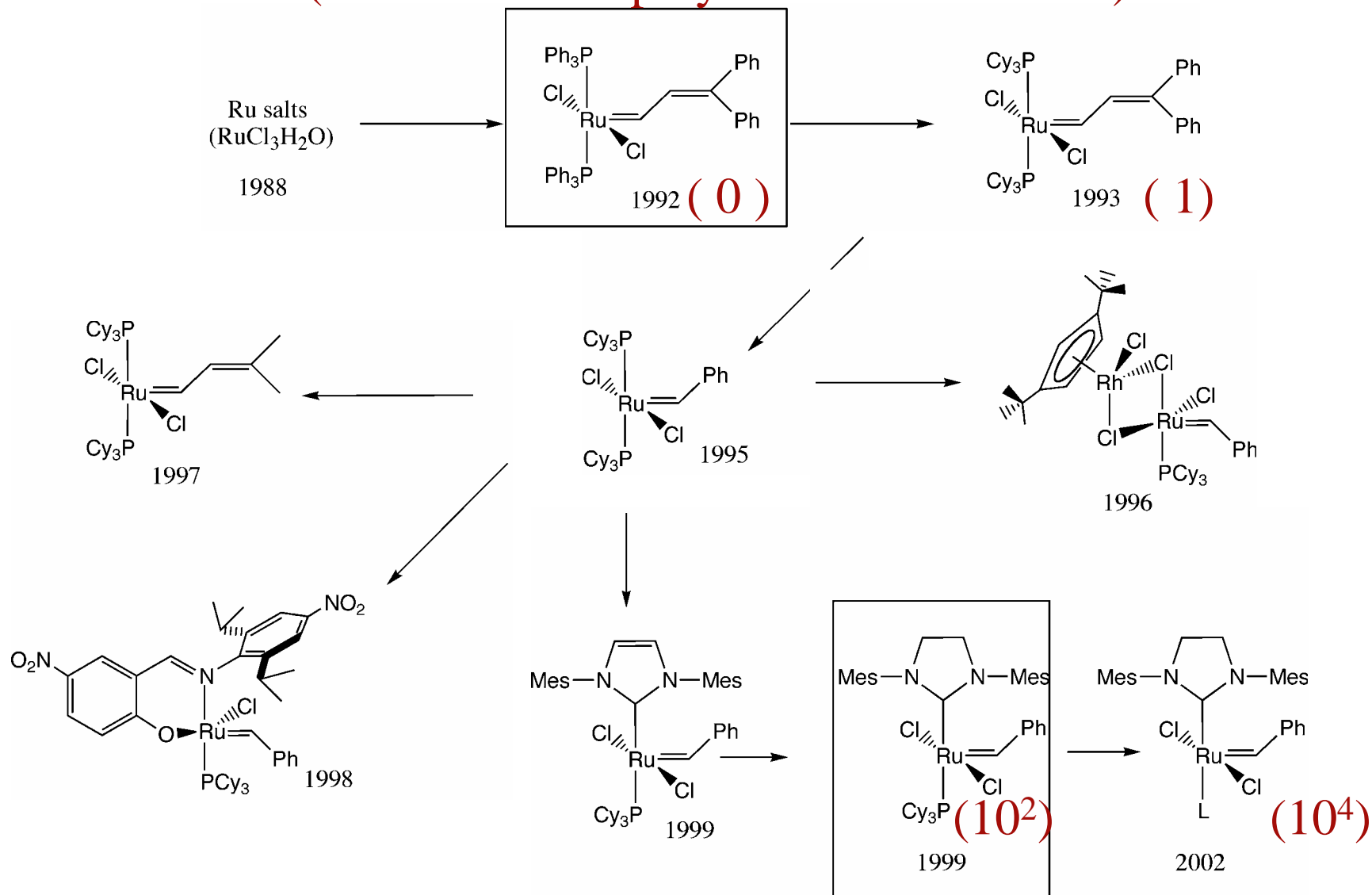


H₂IMes

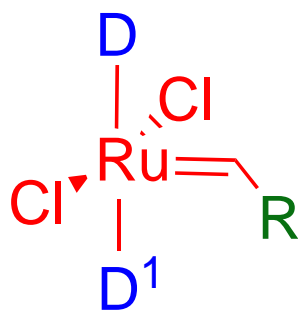
1,3-dimesityl-4,5-dihydroimidazol-2-ylidene

Ru Catalysis Evolution at Caltech

(relative rate of polymerization of COD)



Uses and Applications Resulting from Stable, Tolerant Catalysts

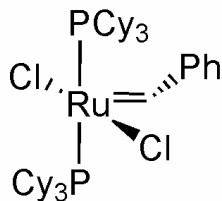


D=2 electron donor

General Catalyst Structure

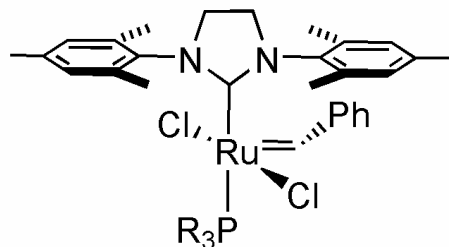
Commercial Ru Catalysts

First Generation

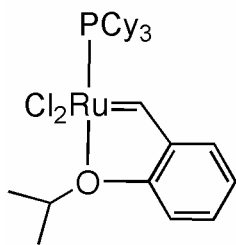


1. Kintically controled products (E:Z)
2. Selective for alkyl substuted double bonds

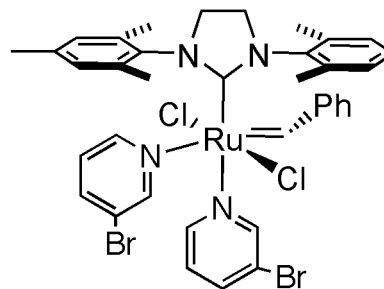
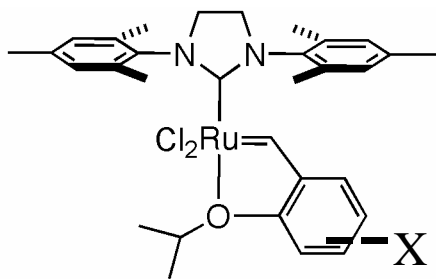
Second Generation



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

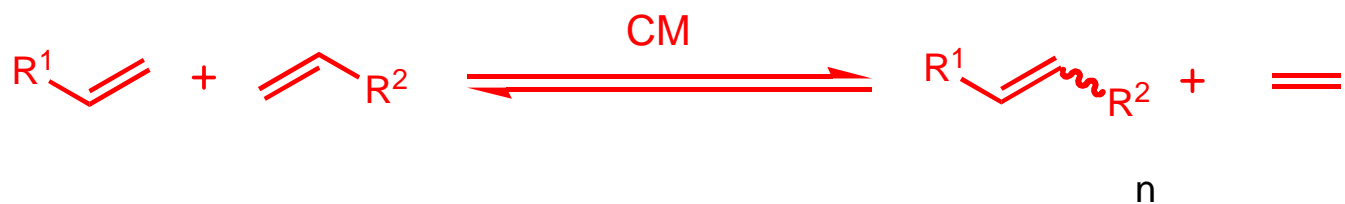


1. Slow initiation
2. Thermally more stable
3. Phosphine free (Hoveyda)

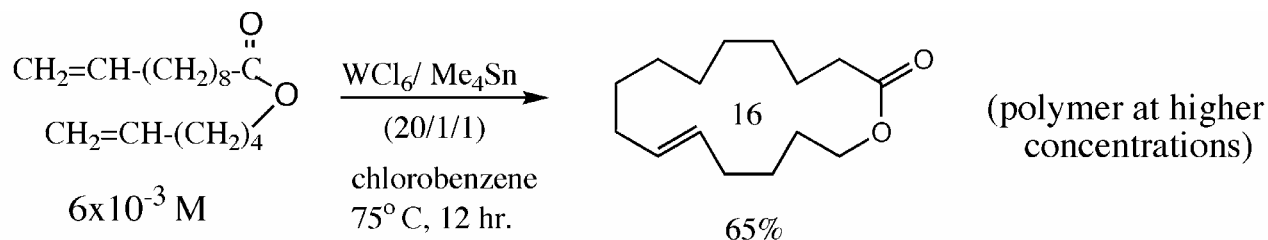


1. Rapid initiation
2. Less thermally stable

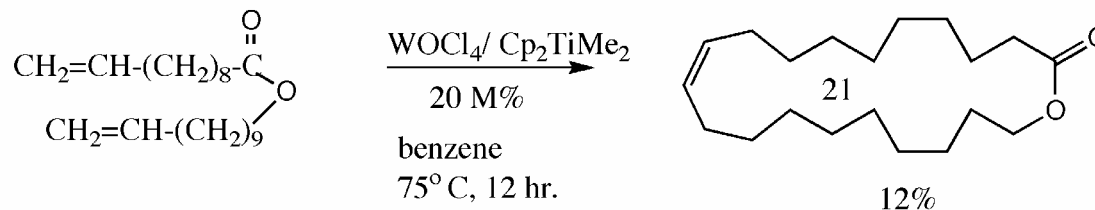
Carbon-Carbon Double Bond Forming Reactions



History of Ring Closing Metathesis



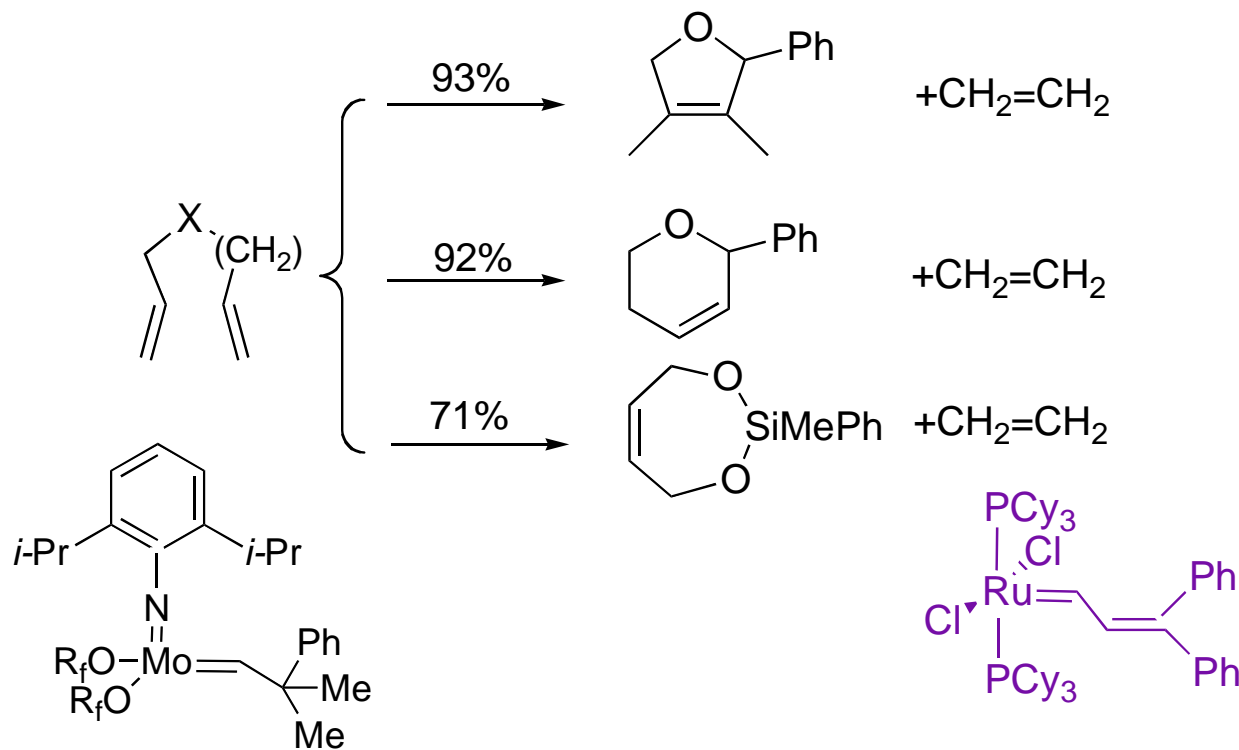
Didier Villemin, *Tetrahedron Letters*, **1980**, 1715



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

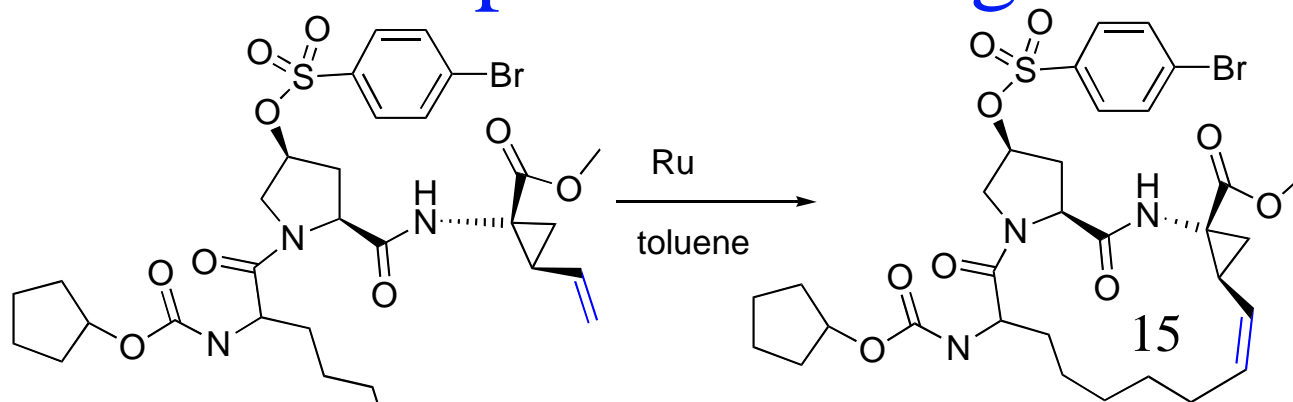


G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, **1992**, *114*, 5426-5427. *J. Am. Chem. Soc.* **1992**, *114* (18), 7324-7325. , *J. Am. Chem. Soc.*, **1993**, *115*, 3800-3801

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

Pharmaceutical Applications

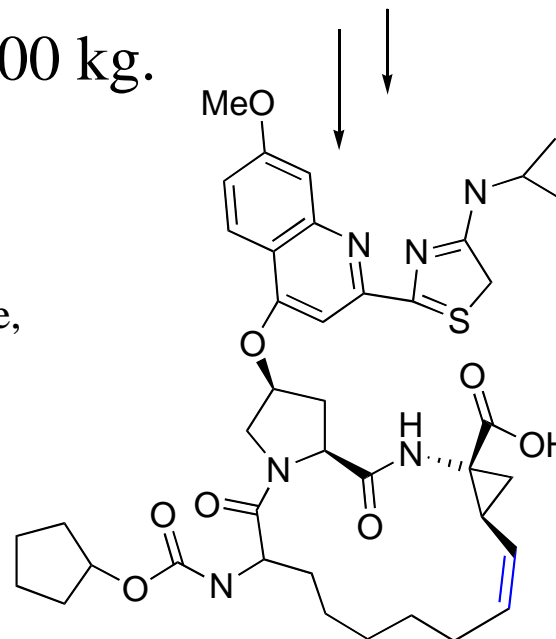
Boehringer Ingelheim Hepatitis C Drugs



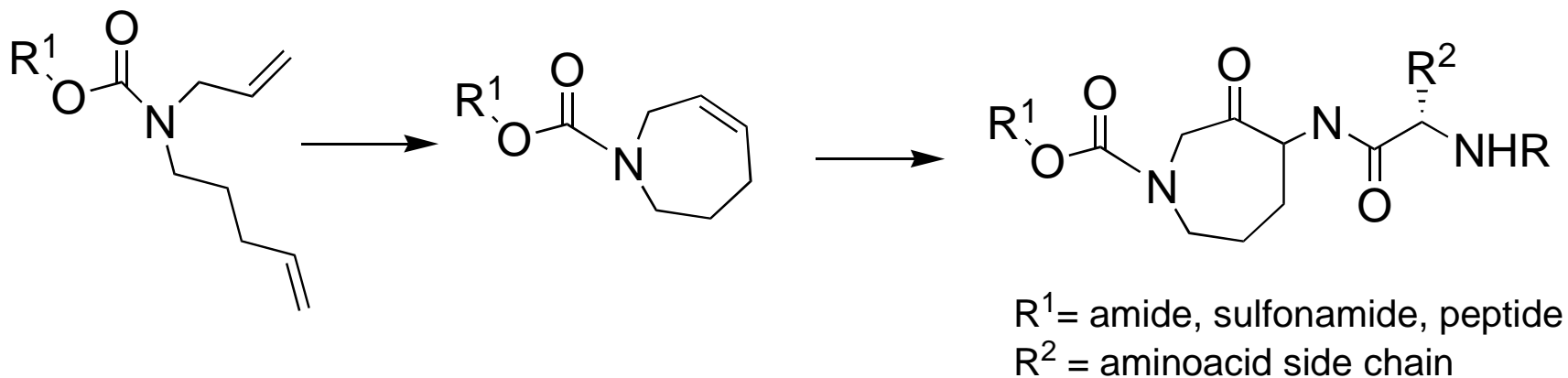
HCV Serine Protease Inhibitor
Boehringer Ingelheim's BILN 2061
Phase II Clinical Trials in US and Europe

400 kg.

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

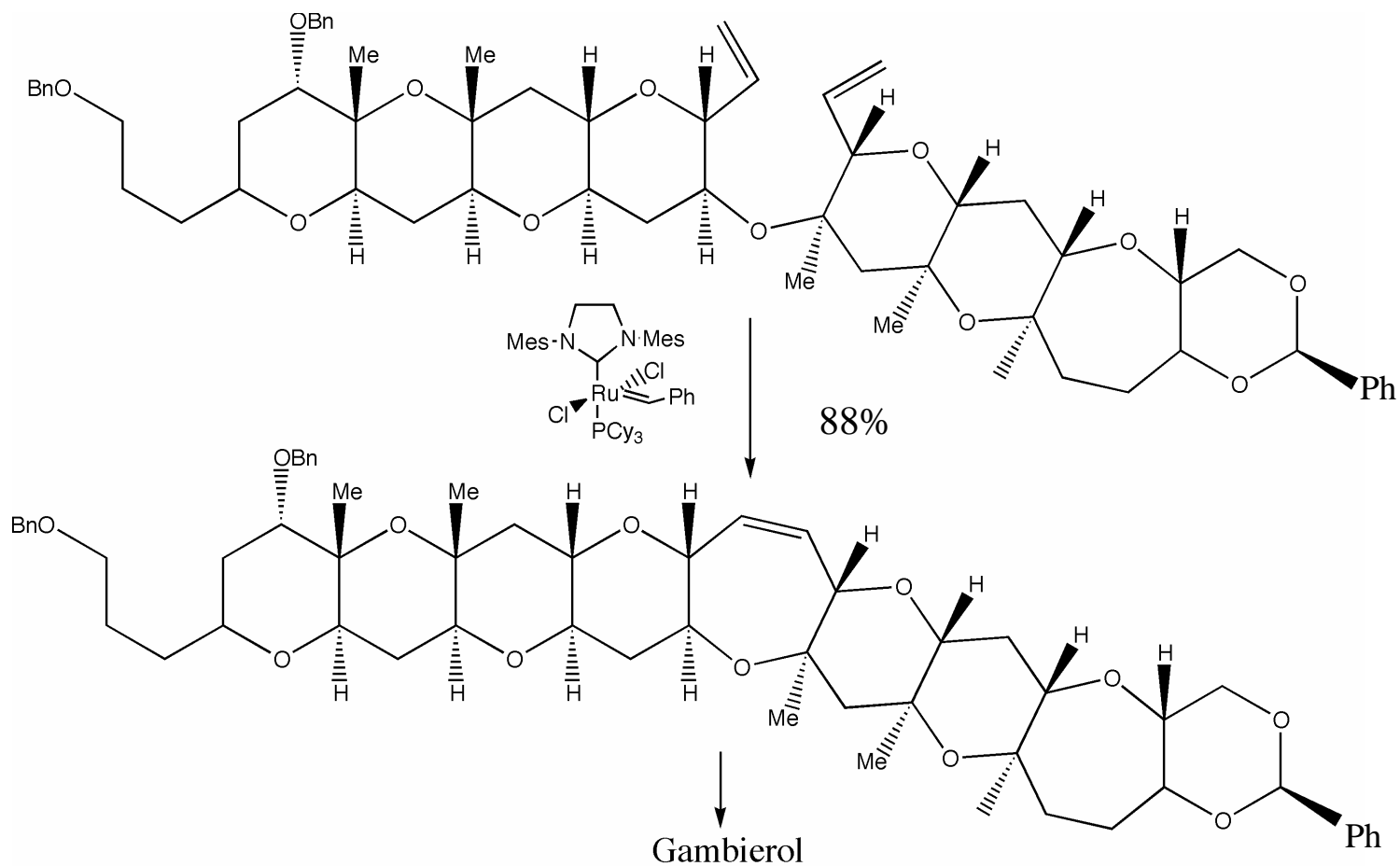


GSK Osteoporosis Drug

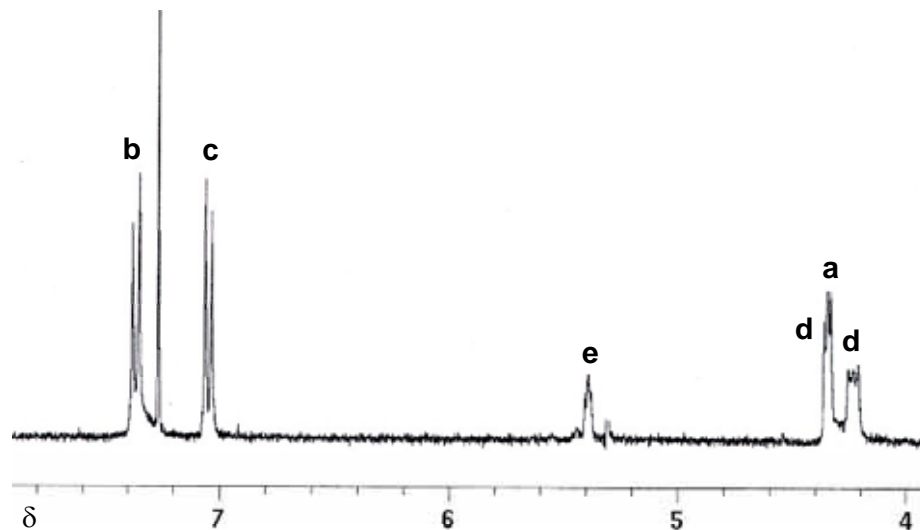
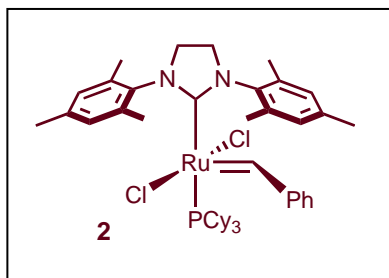
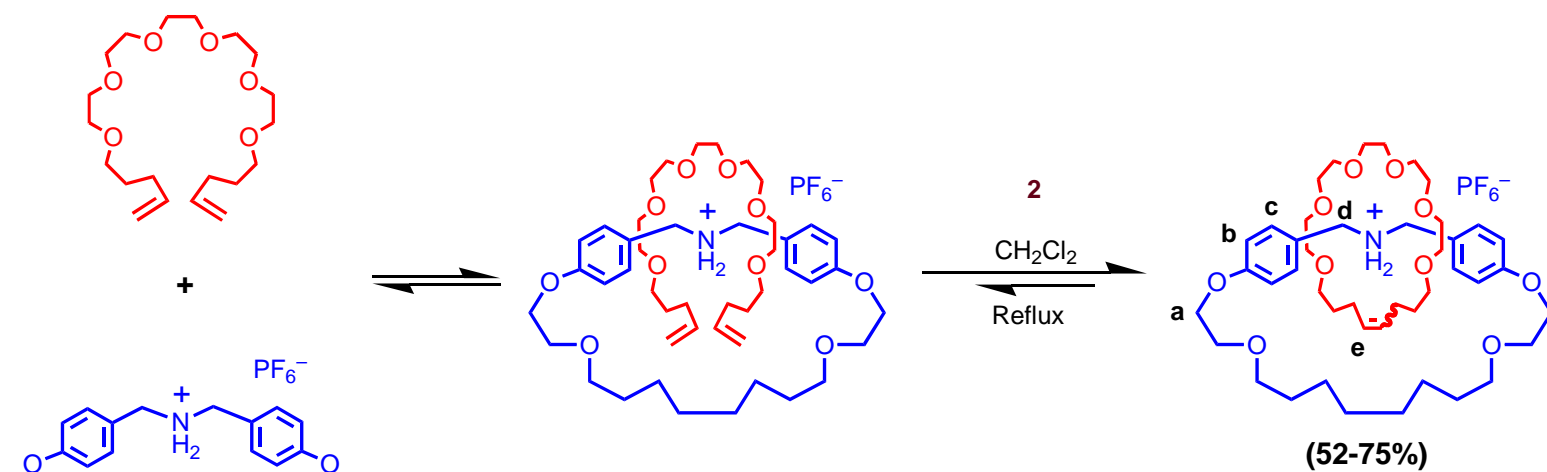


Protease Inhibitor of cathepsin K

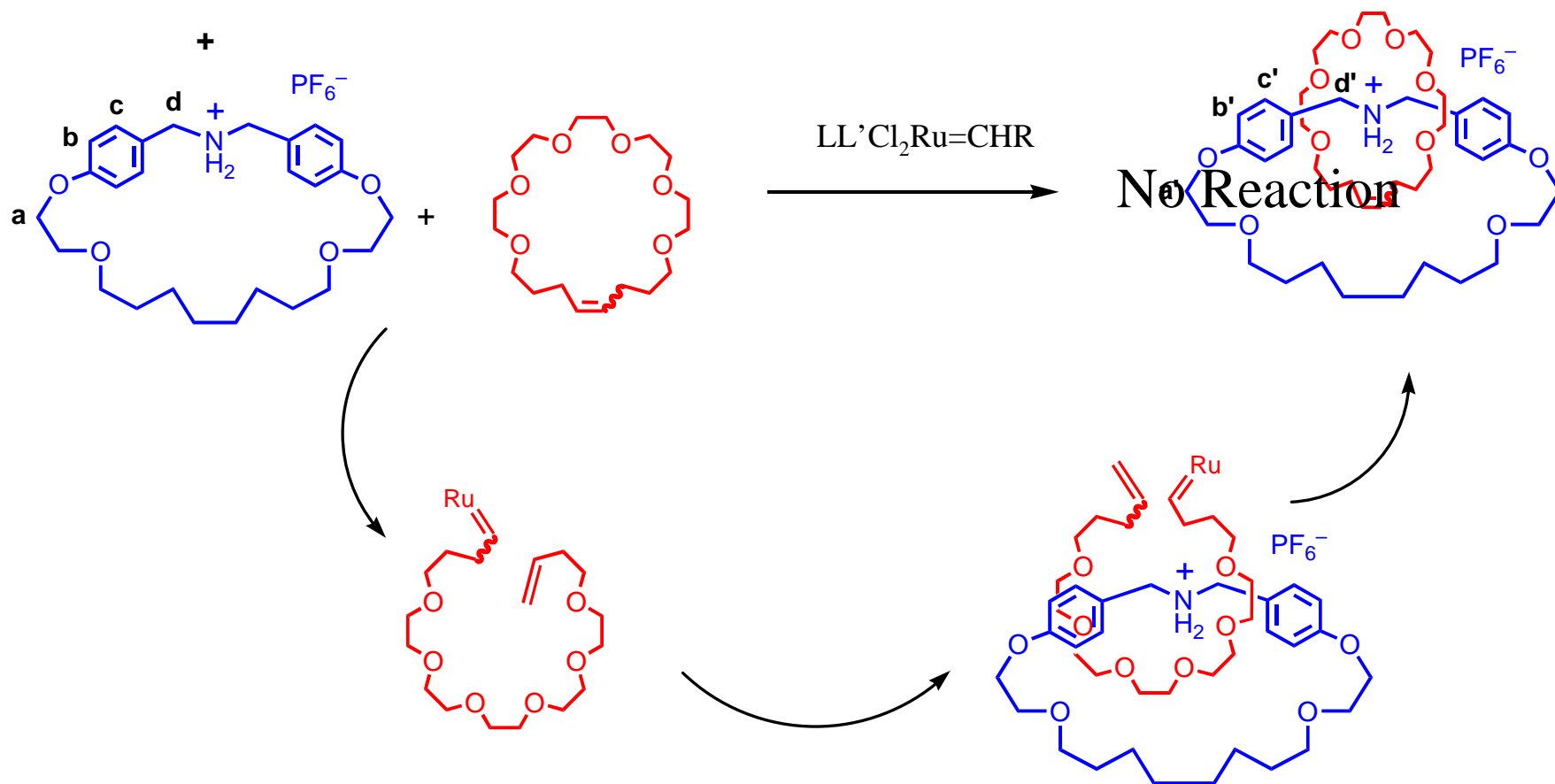
Synthesis of a Large Natural Product



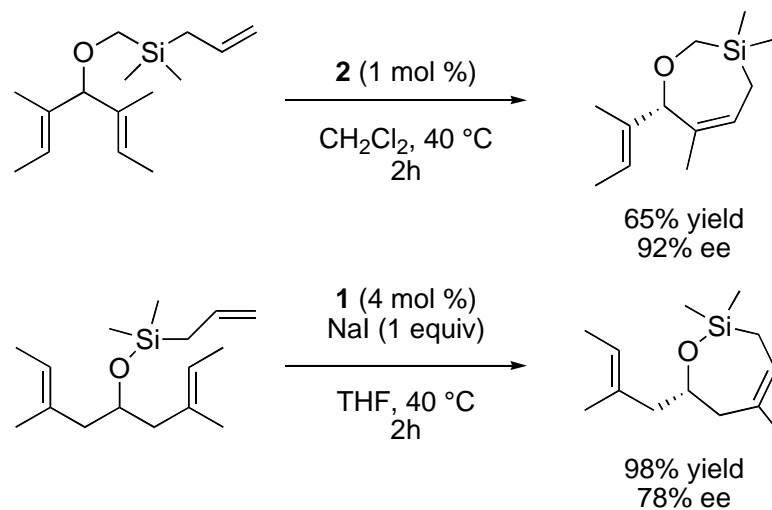
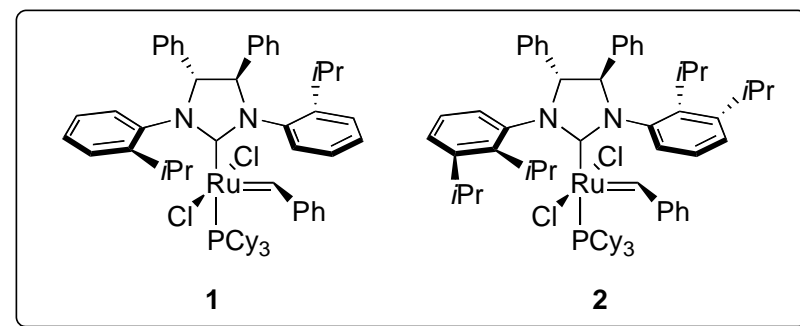
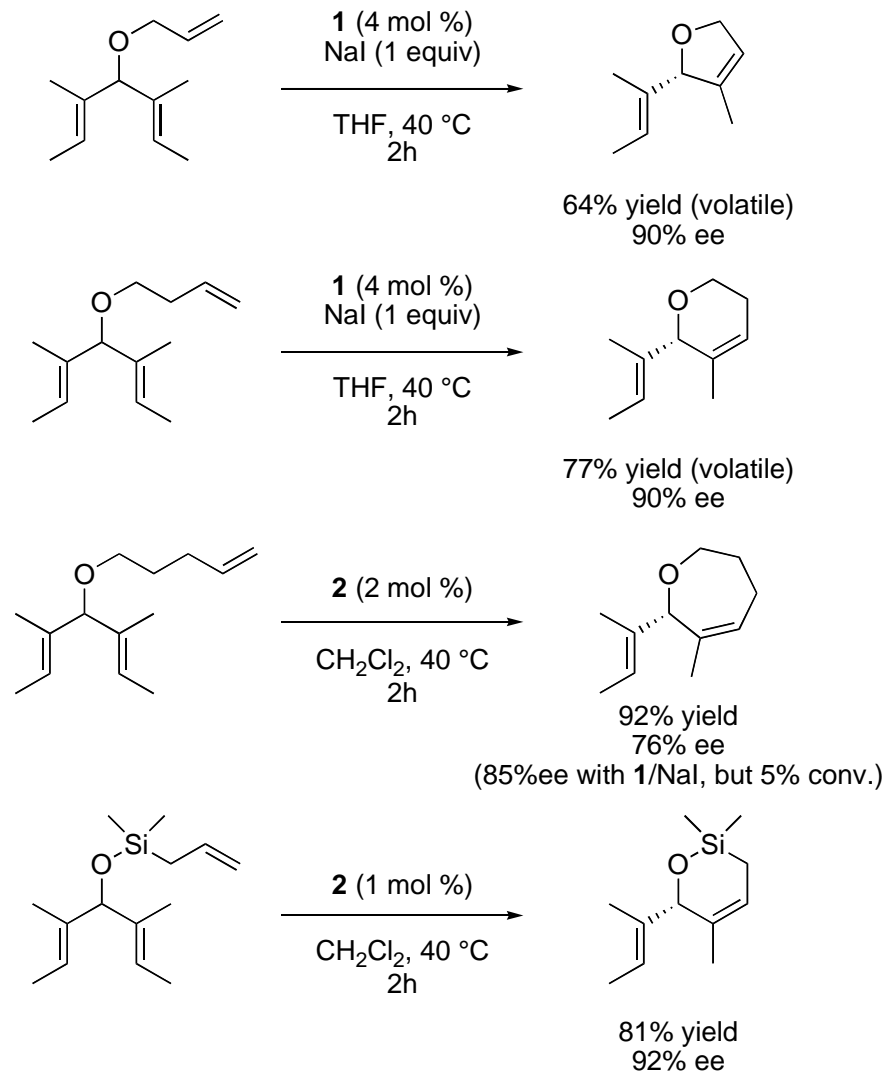
Catenane Formation



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

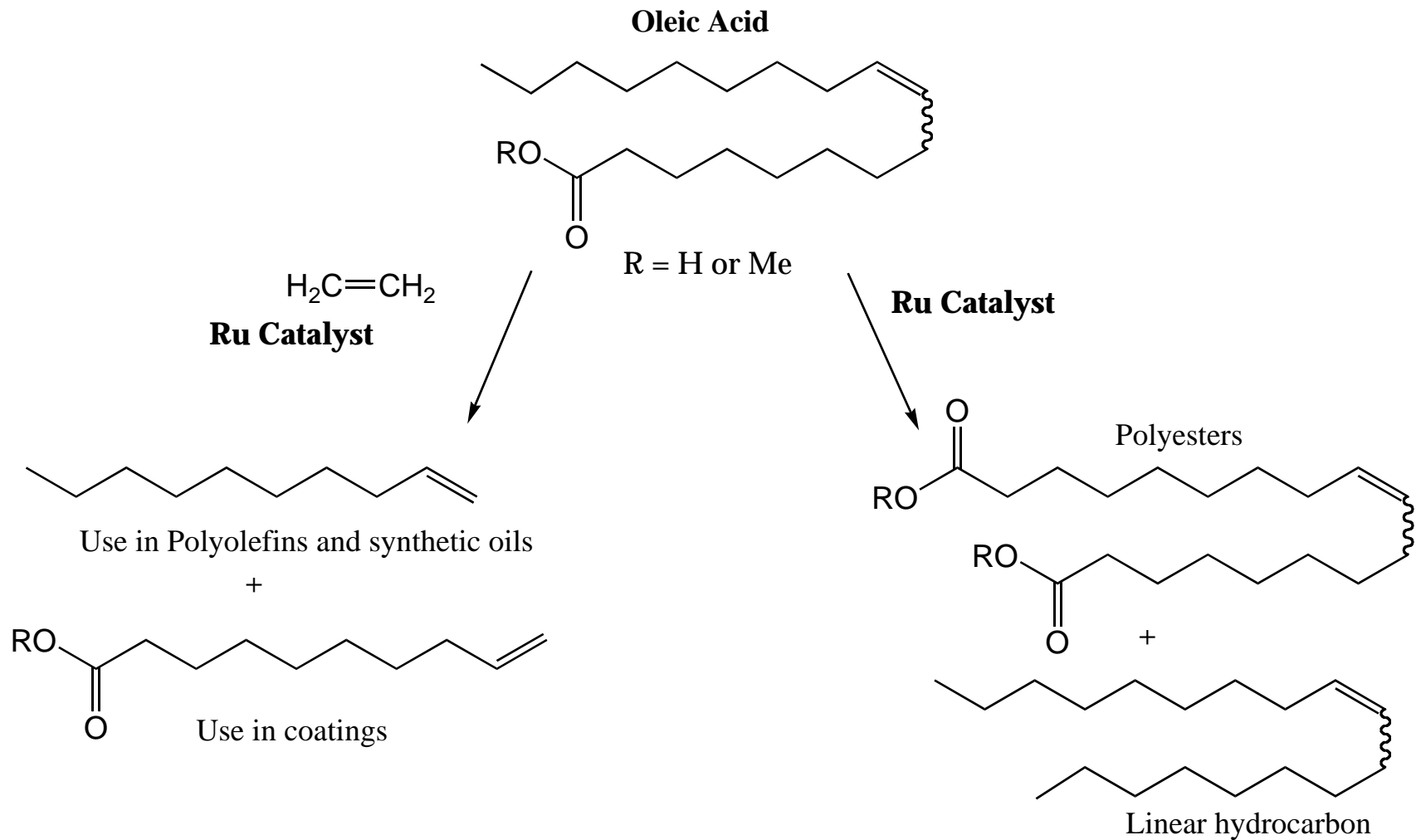
Cargill- Materia- Caltech-DOE

**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**

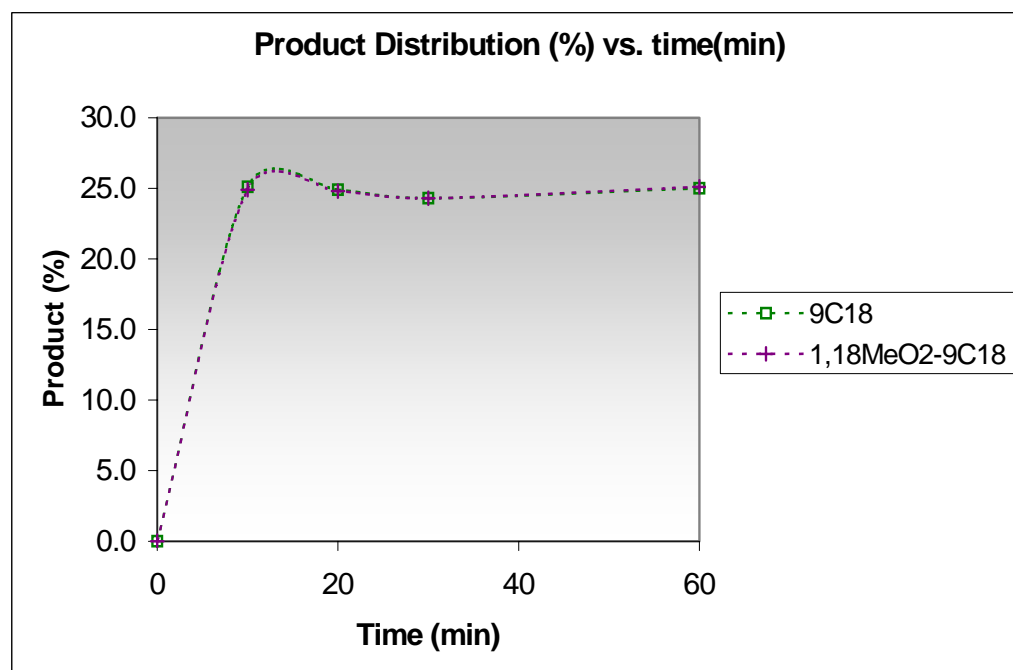
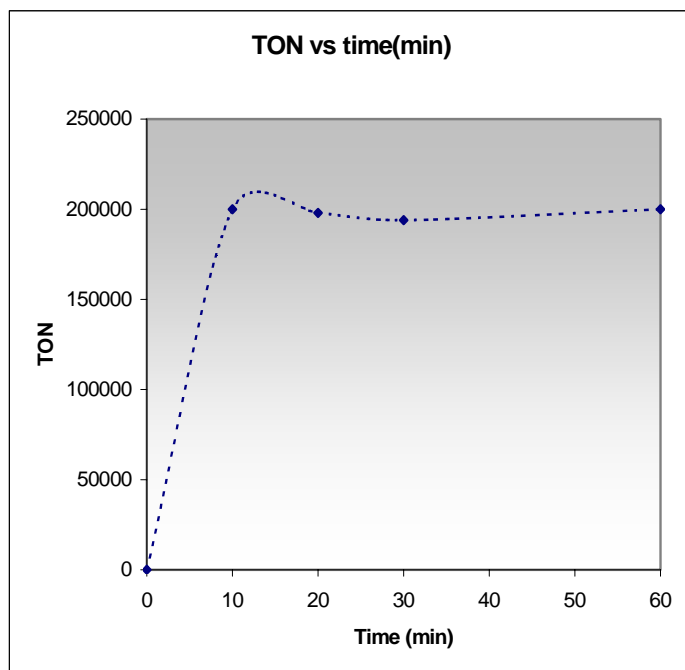
Cargill anticipates that it will have commercial sales in 2006 of several million pounds of a proprietary Ruthenium-metathesis based product derived from a renewable resource that will replace a petroleum-based material.

Oleic Acid to Value Added Chemicals



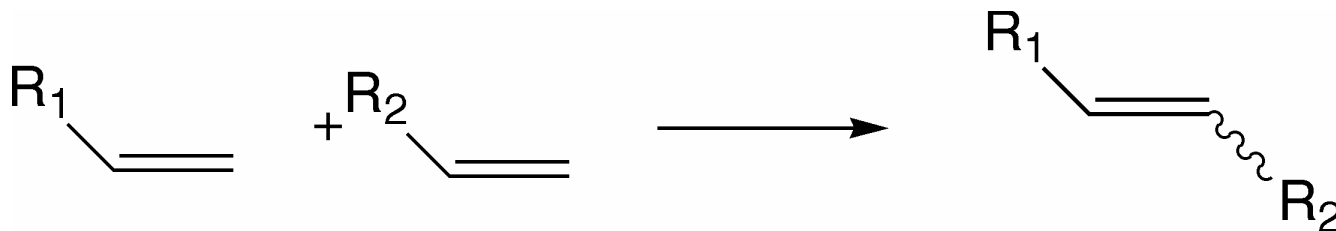
Self-Metathesis of MO: C627 (5 ppm) at 40 °C

Sample #	Time (min)	MO (%)	9C ₁₈ (%)	1,18MeO ₂ -9C ₁₈ (%)	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⁻¹; extremely low impurity formation

Statistical Distribution of CM Products



$R_1 : R_2$ CM yield

1 : 1 50%

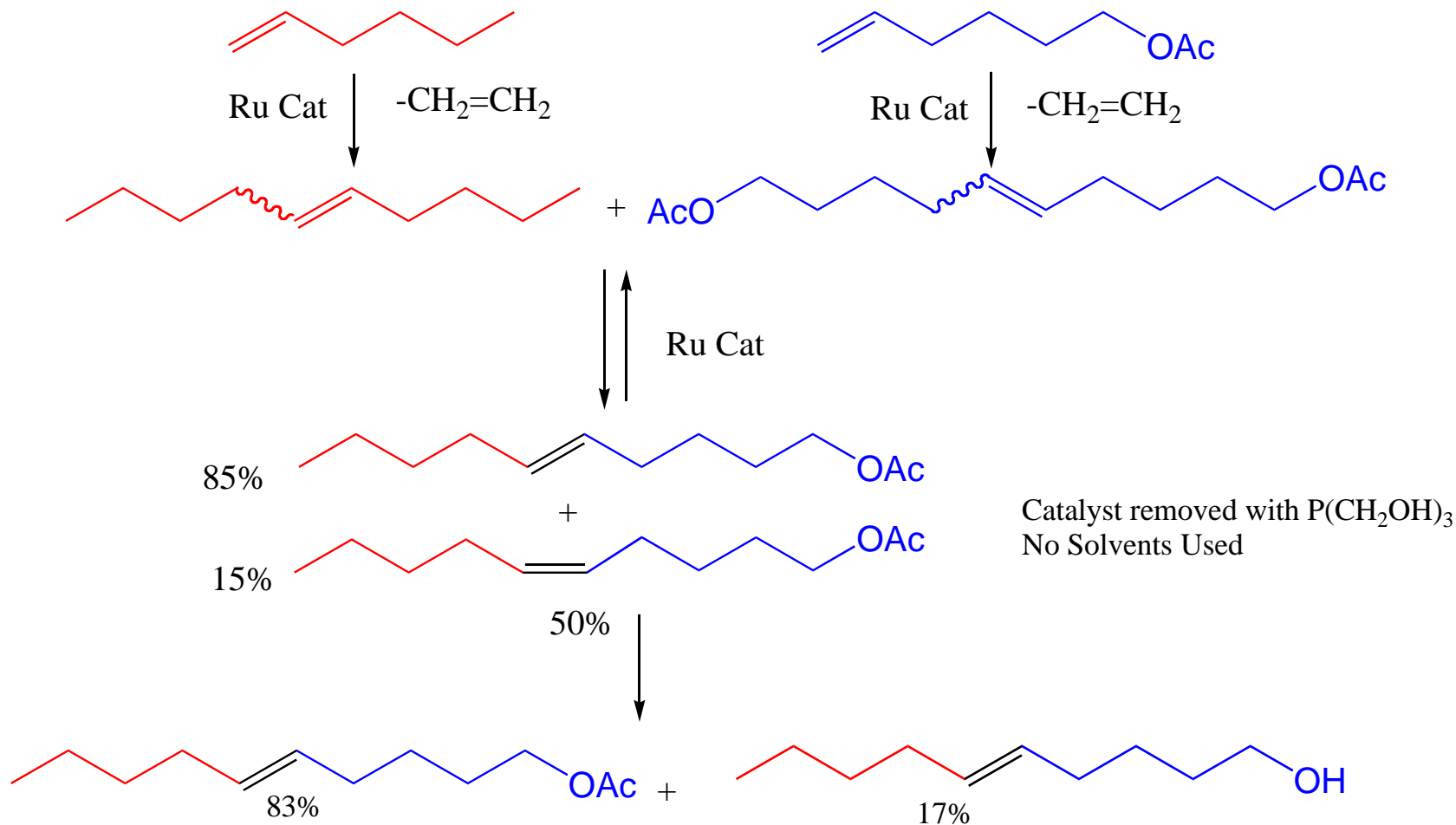
2 : 1 66%

4 : 1 80%

10 : 1 91%

20 : 1 95%

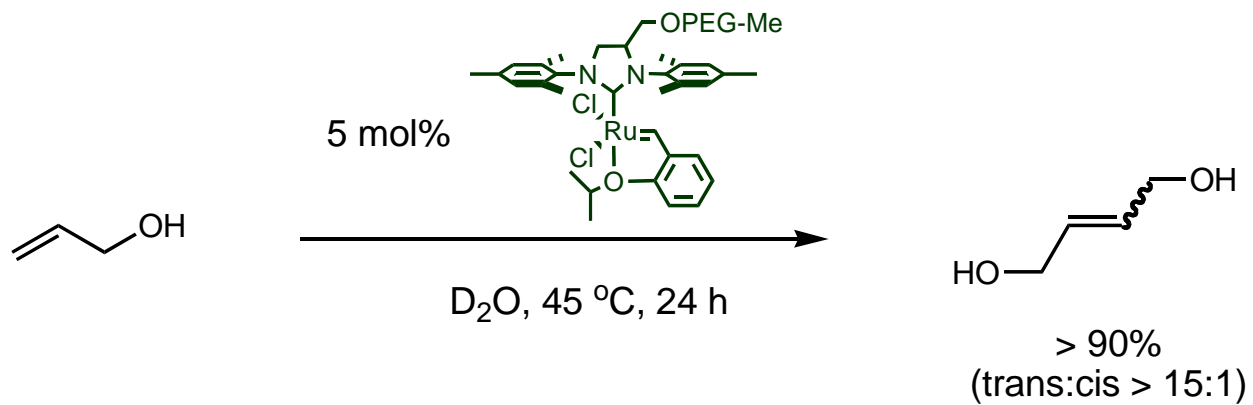
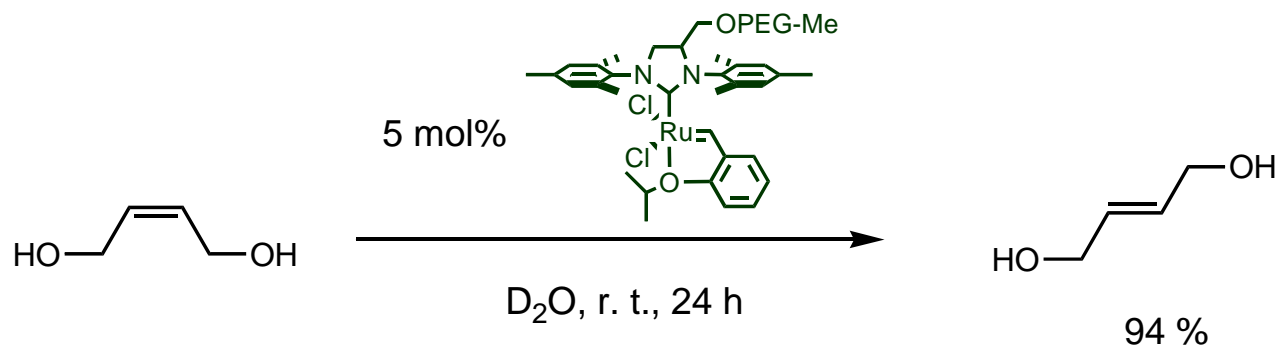
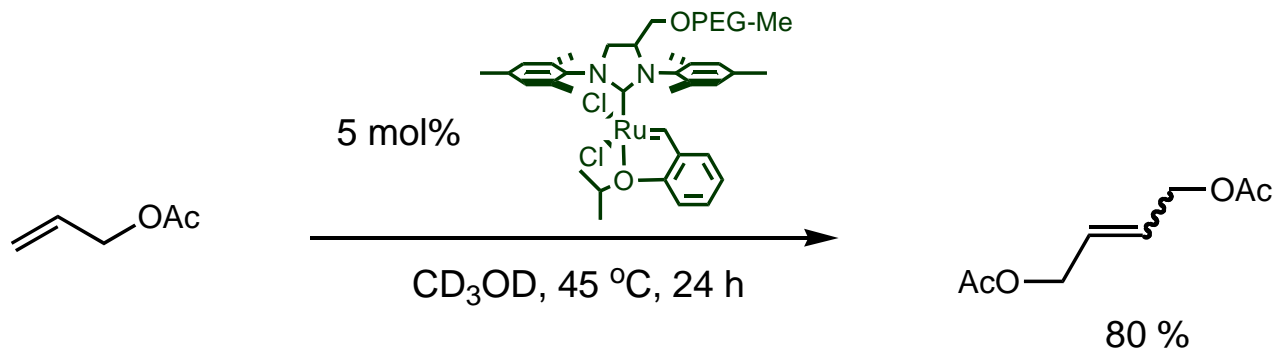
Pheromone by Cross Metathesis



PHEROMONE for Peach Twig Borer
Used in Mating Disruption

Water as a Solvent

Cross Metathesis

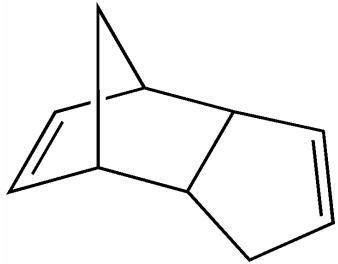


Polymer Synthesis

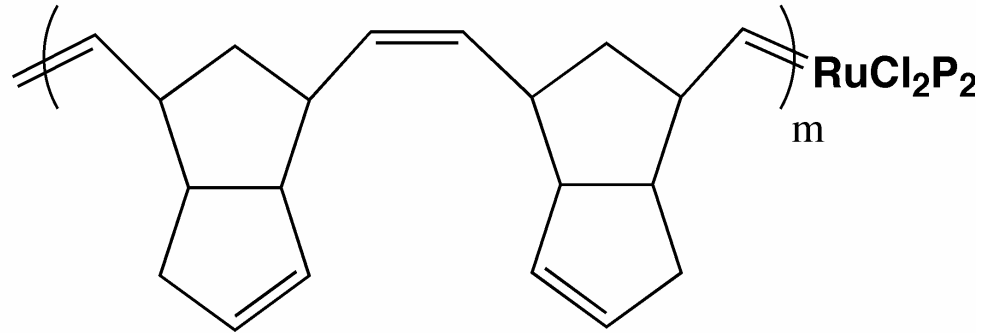
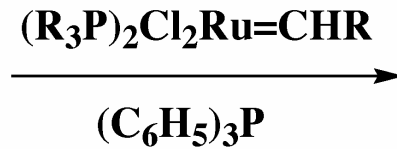
Mechanical Properties

Chemical Function

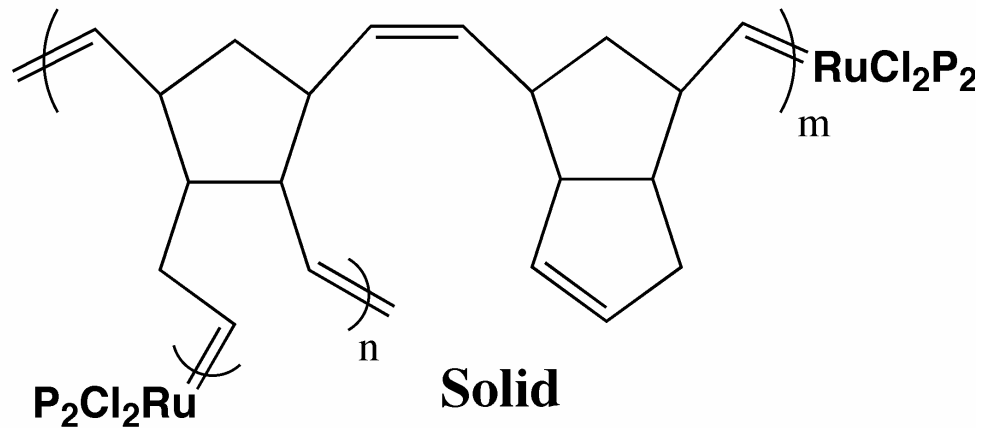
Dicyclopentadiene-Thermoset Polymer



Liquid



Cross-link



Solid

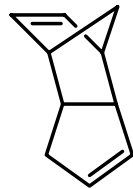
$T_g > 120^\circ C$ E-modulus > 2000 MPa

Impact > 10 psi

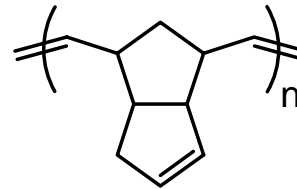
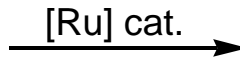
PolyDCPD-9mm Ballistic Protection



Products Made With DCPD ROMP



DCPD



poly(DCPD)



Consumer products



Truck Parts



Sports Equipment

www.plastictechnology.com
baseball.eastonsports.com

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