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

$$n\ CH_2{=}CH_2 \xrightarrow{AlEt_3} H\text{-}(CH_2\text{-}CH_2)_n\text{-}CH{=}CH_2$$

n= 1-12

1950+

$$n\ CH_2{=}CH_2 \xrightarrow[Ni]{AlEt_3} CH_3\text{-}CH_2\text{-}CH{=}CH_2$$

only !

1953

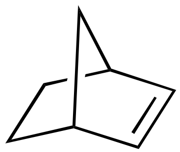
$$n\ CH_2{=}CH_2 \xrightarrow[\text{room temperature, low pressure}]{TiCl_4/AlR_3} \left(CH_2-CH_2\right)_n$$

Called High density polyethylene -HDPE density=0.97

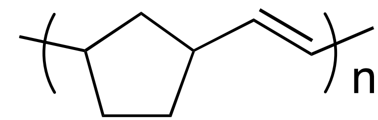
Crystalline - Milk bottles

K. Ziegler and G. Natta, Nobel Prize 1963

Discovery of a New Reaction



Ziegler catalyst $TiCl_4/AlR_3$ ⟶ Polymer containing unsaturation- unexpected for an addition polymer



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

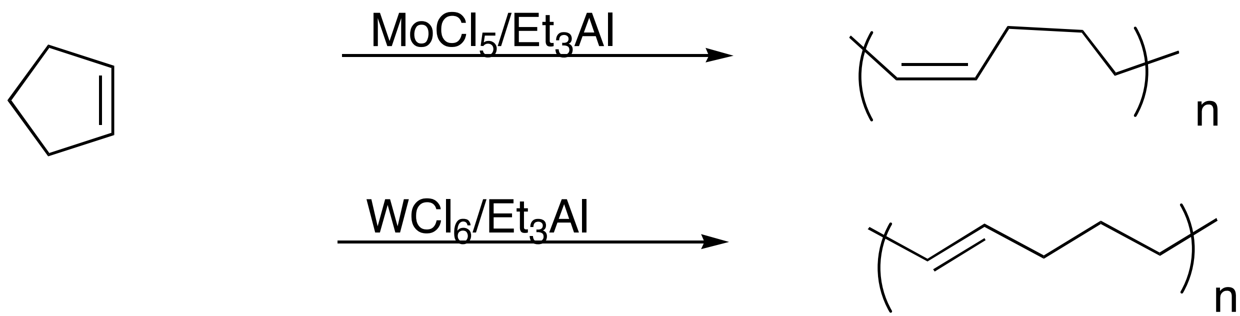
$$2\ CH_2{=}CHCH_3 \xrightarrow{Co/MoO_n} CH_2{=}CH_2 + CH_3CH{=}CHCH_3$$

Three carbons — Two carbons — Four carbons

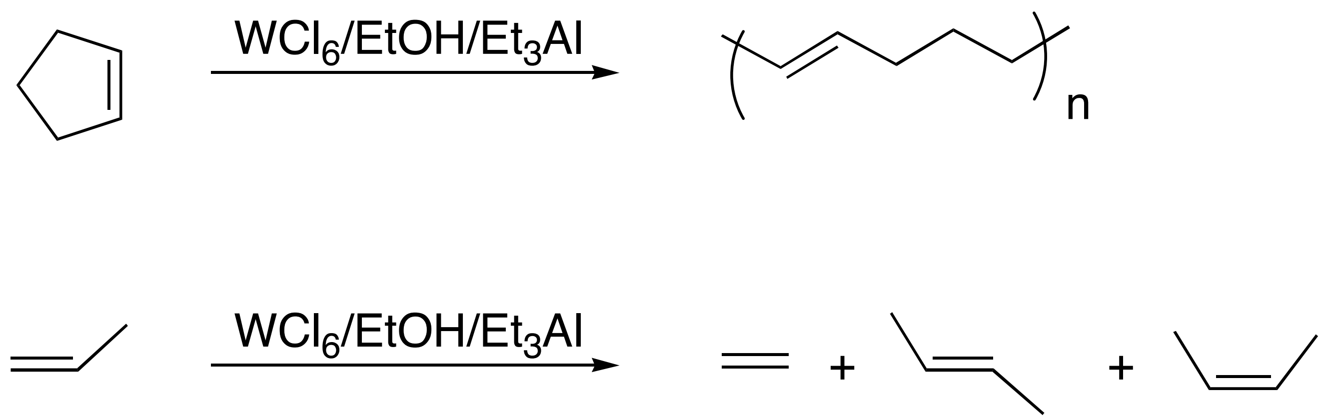
Heterogeneous Catalyst

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

Metathesis Discovery



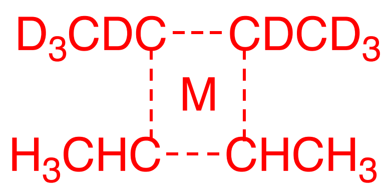
Natta, et. al. J. Polymer Sci., Polymer Lett. 1964, B2, 349



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

Proposed Mechanisms

$CD_3CD{=}CDCD_3$ + $CH_3CH{=}CHCH_3$ $\xrightarrow[\text{catalyst}]{\text{metathesis}}$ $CD_3CD{=}CHCH_3$



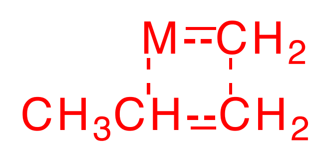
Proposed intermdiate

$CD_3CH{=}CHCH_3$
$CD_3CD{=}CDCH_3$
$CD_3CH{=}CHCD_3$
$CH_3CD{=}CDCH_3$
Not Observed

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

$CH_3CH{=}CH_2 \longrightarrow CH_2{=}CH_2 + CH_3CH{=}CHCH_3$

$CH_3CH{=}CH_2 + M{=}CH_2 \longrightarrow CH_2{=}CH_2 + M{=}CHCH_3$

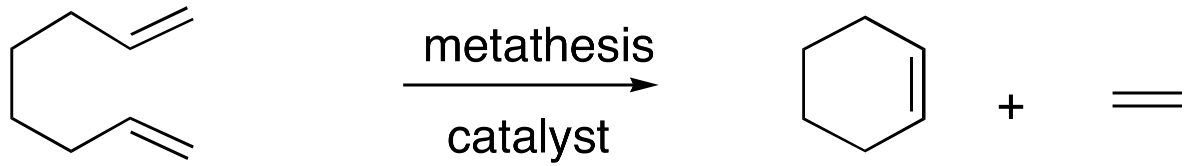


Proposed Intermediate

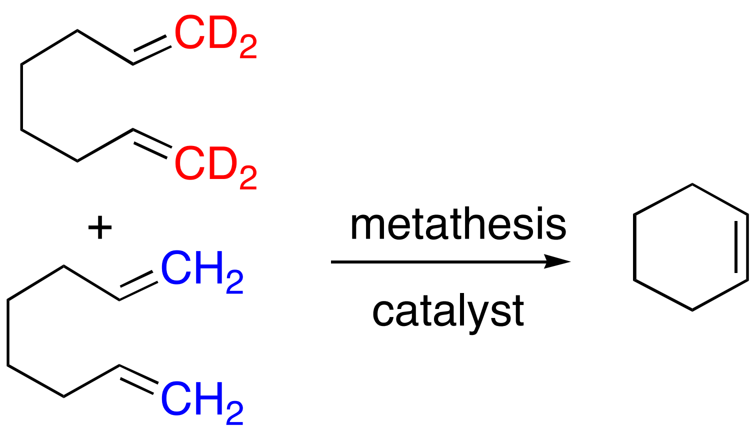
$CH_3CH{=}CH_2 + M{=}CHCH_3 \longrightarrow CH_3CH{=}CHCH_3 + M{=}CH_2$

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



metathesis inactive



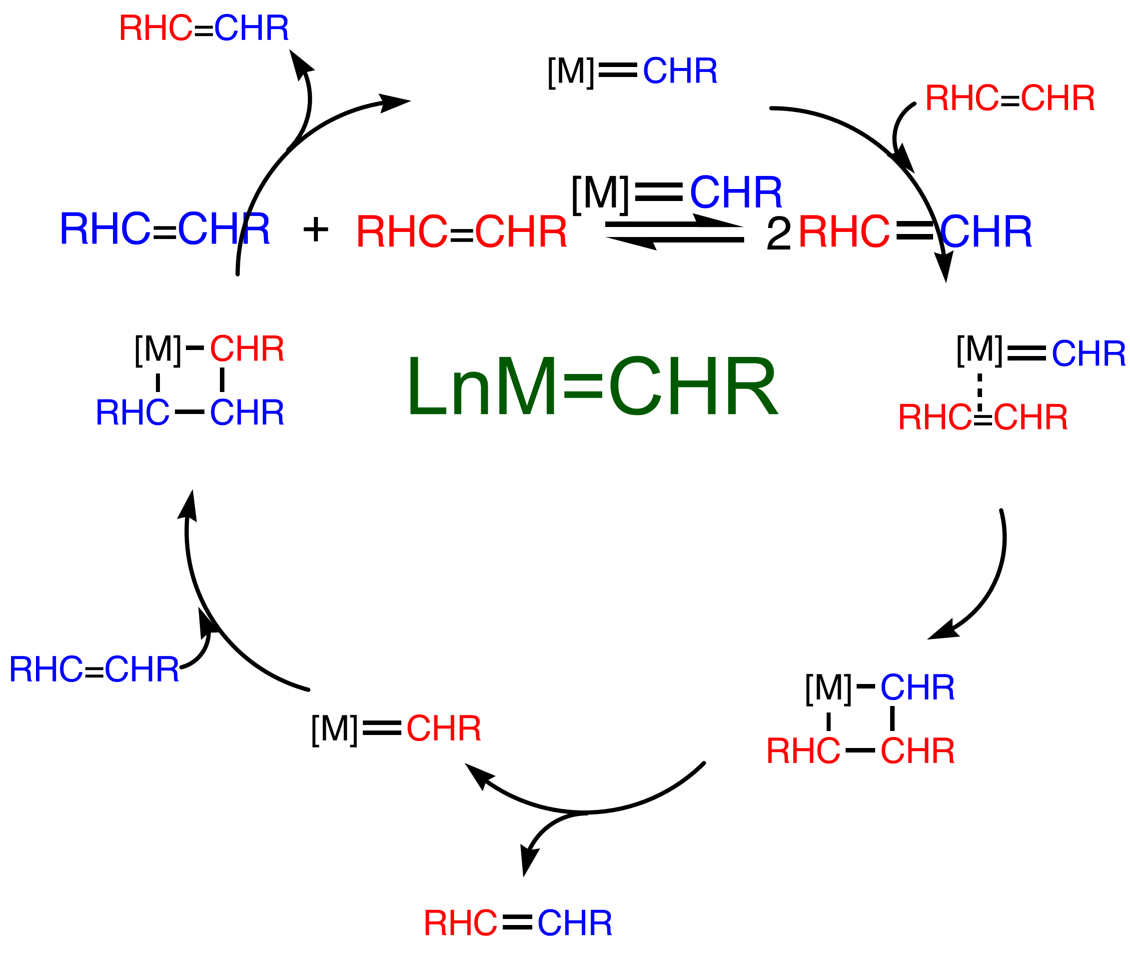
predicted Ratio

	Chauvin	pairwise
$D_2C{=}CD_2$	1	1
+ $H_2C{=}CD_2$	2	0 (1.6)
+ $H_2C{=}CH_2$	1	1

OBSERVED (Chauvin)

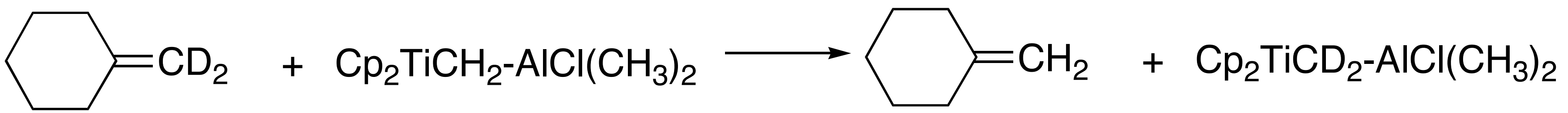
R. H. Grubbs, P. L. Burk and D. D. Carr, *J. Am. Chem. Soc.* **1975**, *97,* 3265.
T. J. Katz and R. Rothchild, *J. Am. Chem. Soc.* **1976**, *98,* 2519.

Olefin Metathesis Mechanism



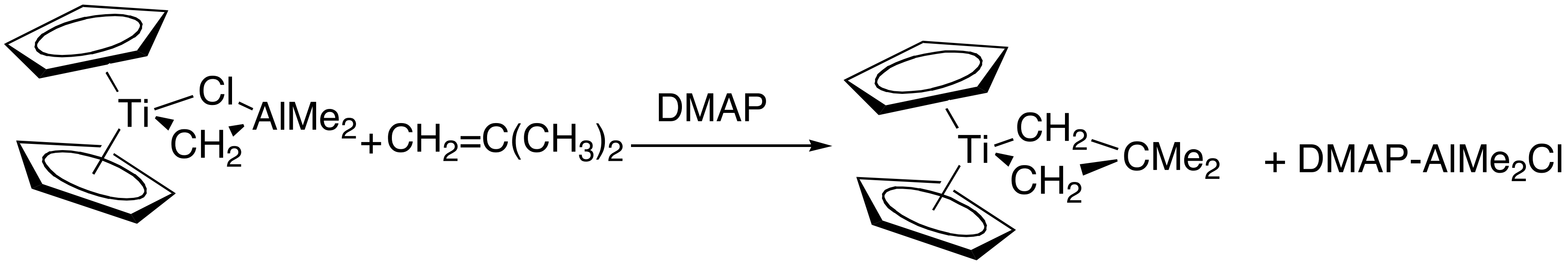
Carbene Catalysts

Demonstration of Exchange between Metal Methylene and an Olefin



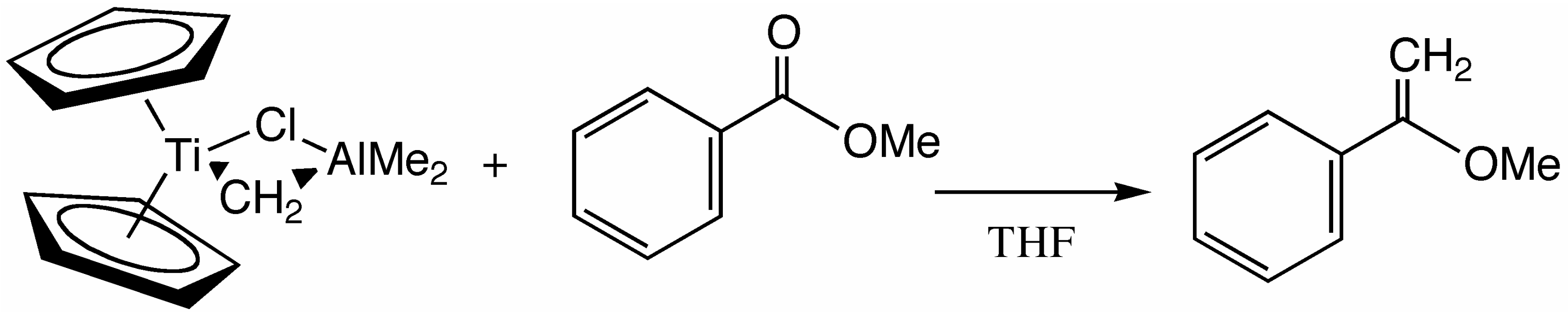
F.N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978,** *100,* 3611

Isolation of Metallacycle in Active Metathesis System



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

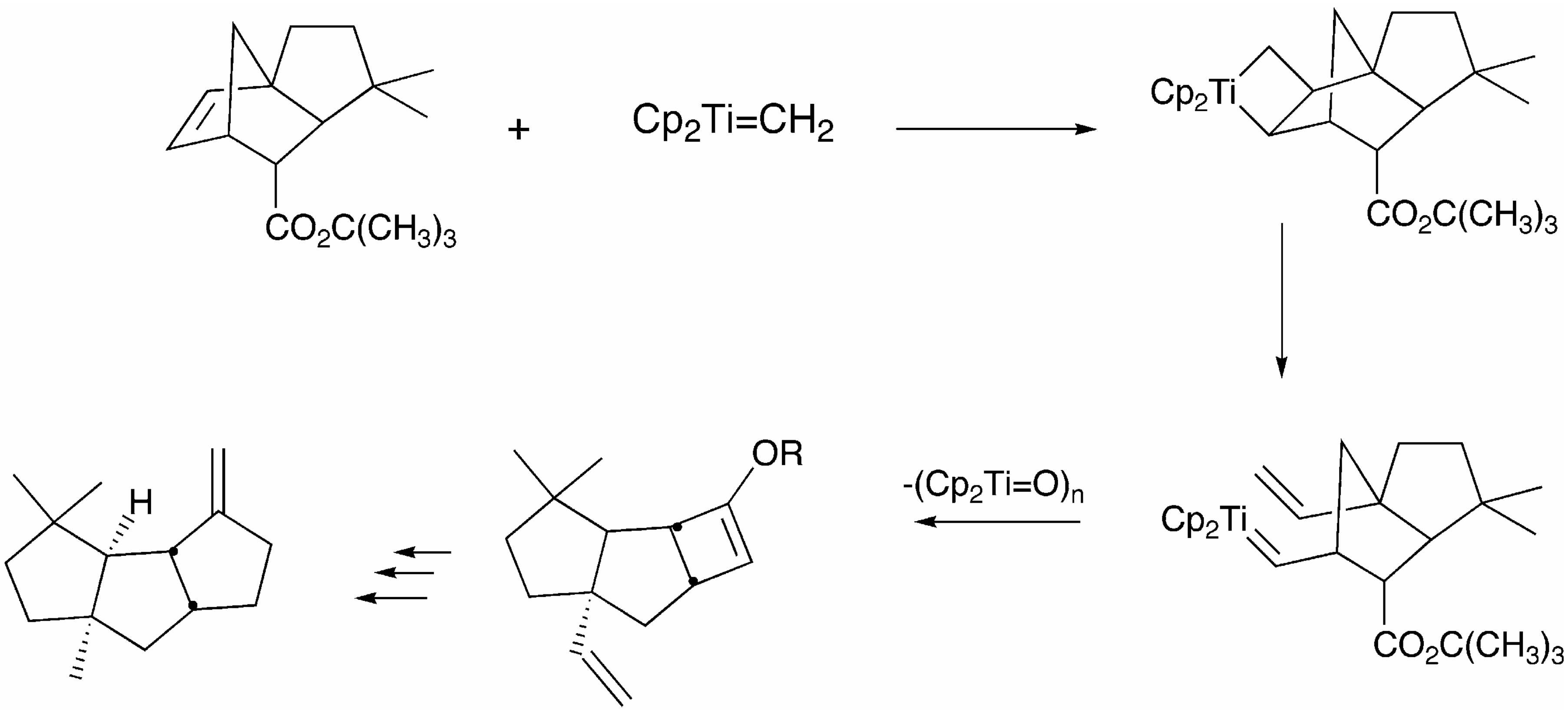
Tebbe Reagent



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

Metal Alkylidenes in Organic Synthesis

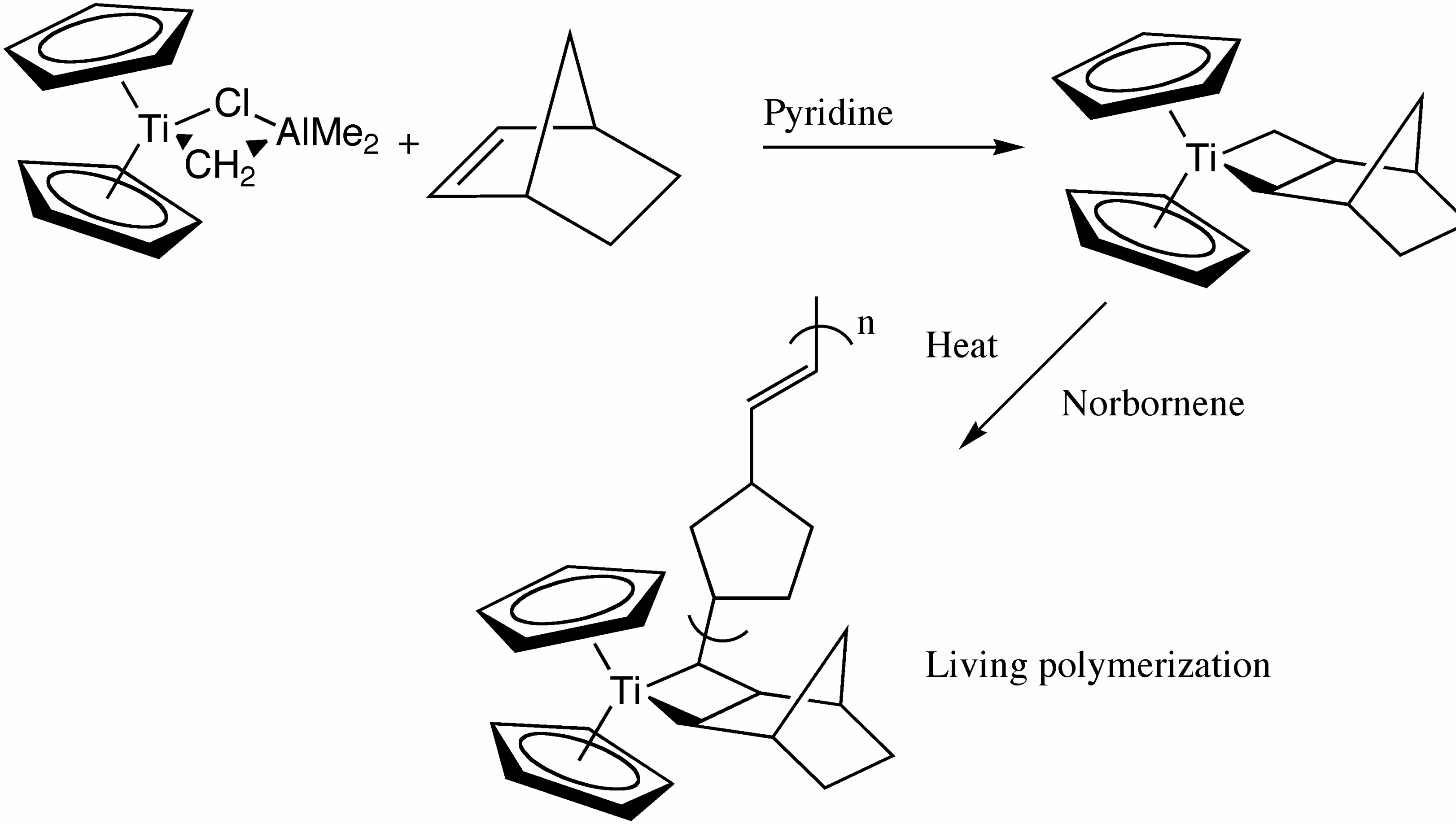
Tebbe Reagent in Synthesis



△ (9,12) -Capnellene

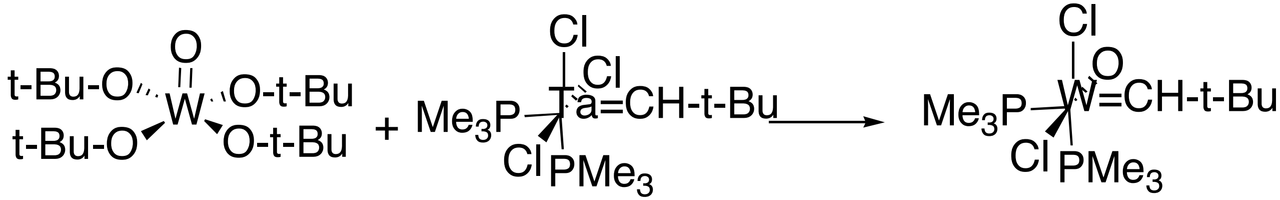
John R. Stille and R. H. Grubbs, *J. Am. Chem. Soc.*, **1986**, *108*,855

Living ROMP Polymers



L. R. Gilliom and R. H. Grubbs, *J. Am. Chem. Soc.* **1986**, *108*, 733.

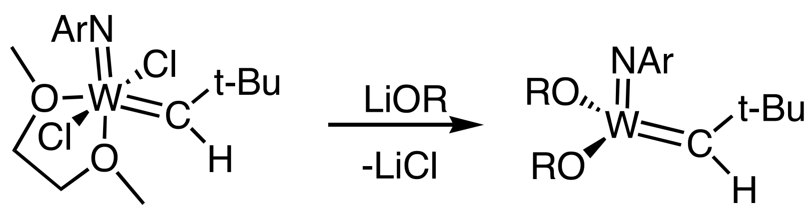
Schrock Alkylidenes



Active with $AlCl_3$

with terminal olefins $W{=}CH_2$ complex observed

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



Activity depends on R

$[(CF_3)_2CH_3]CO^- \gg (CH_3)_3CO^-$

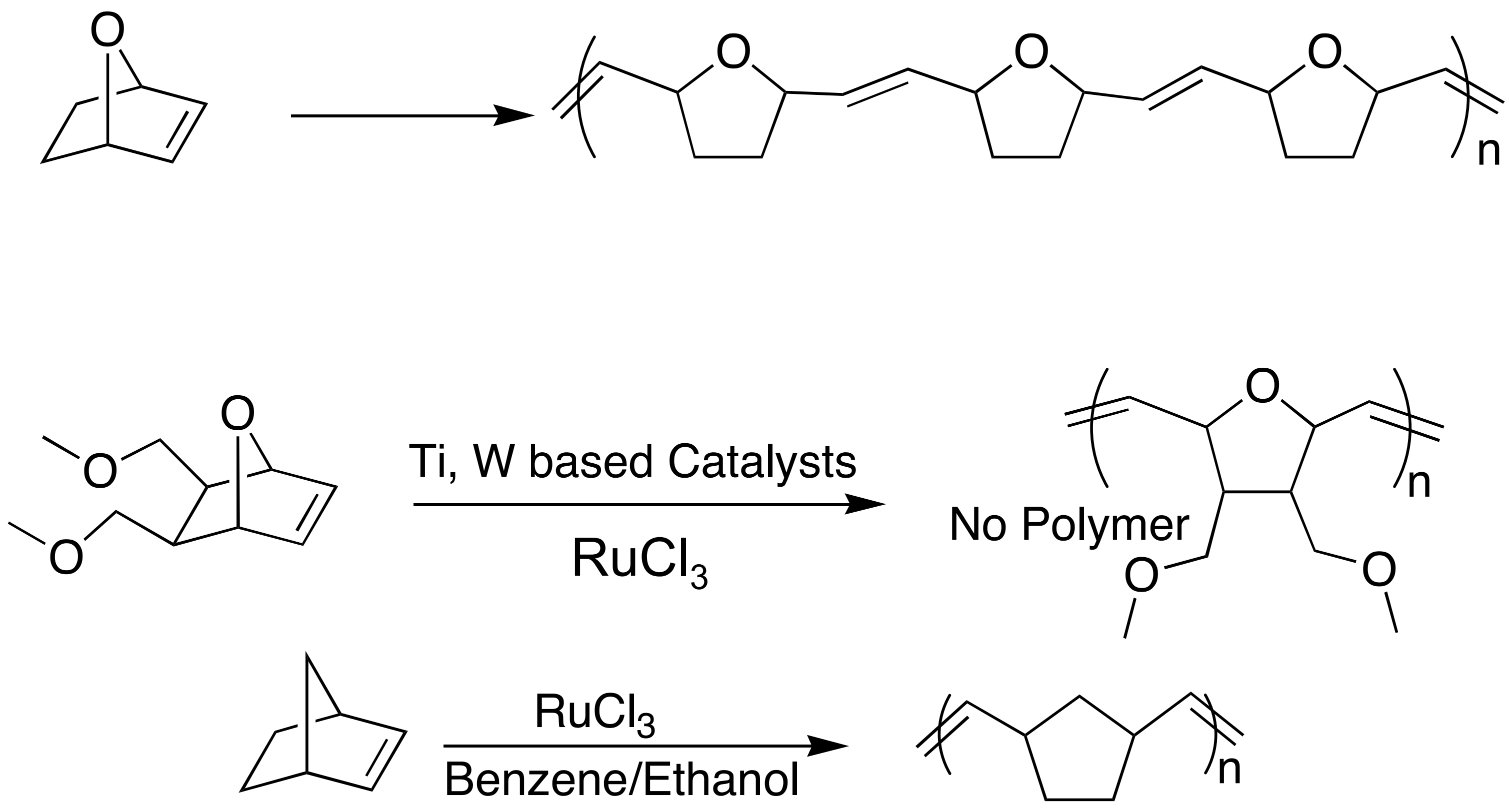
also Mo
Analog

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 catalylsts)

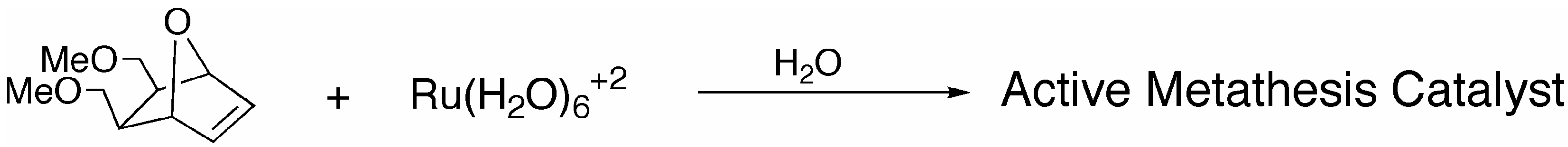
The Ruthenium Story

Synthesis of an Ionophore



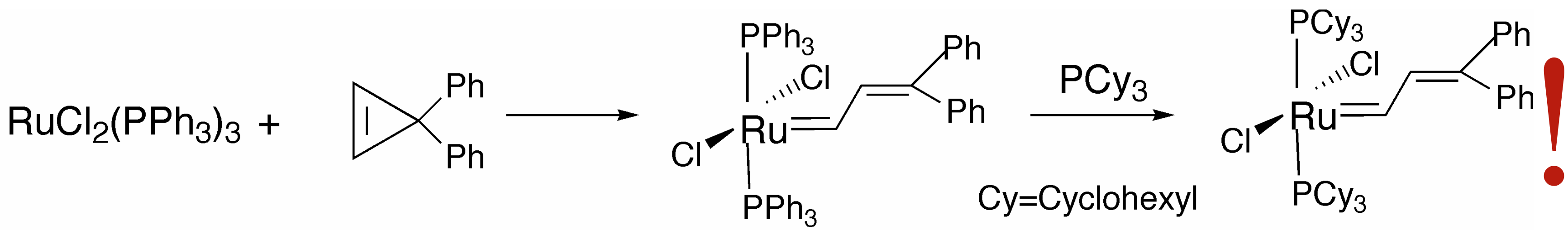
F. W. Michelotti, W. P. Keaveney, *J. Poly. Sci., Part A,* **1965,** 895

Ruthenium Catalyst Synthesis



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

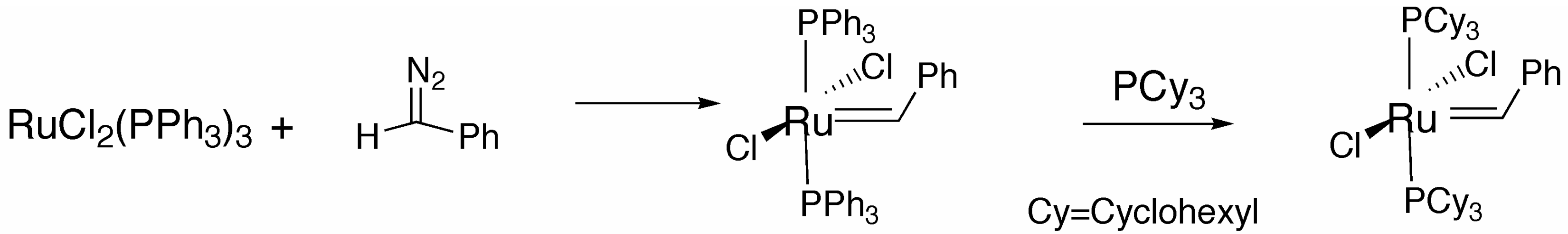
Ill defined, highly active, little initiation



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

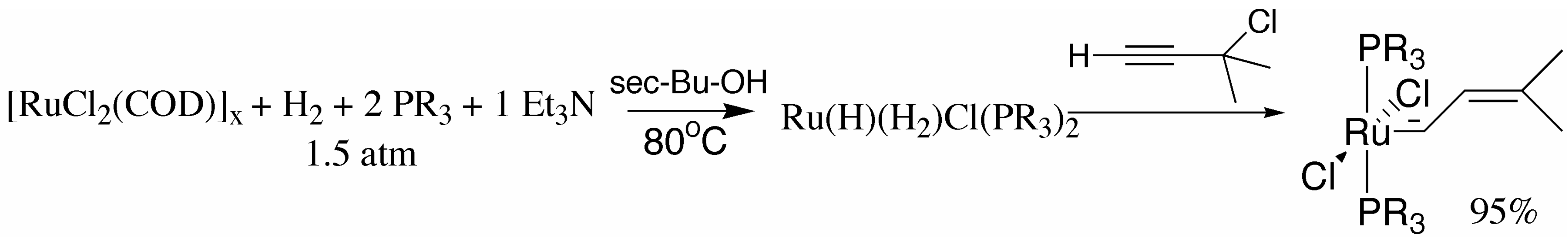
Well defined, good activity, 100mg/week

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.

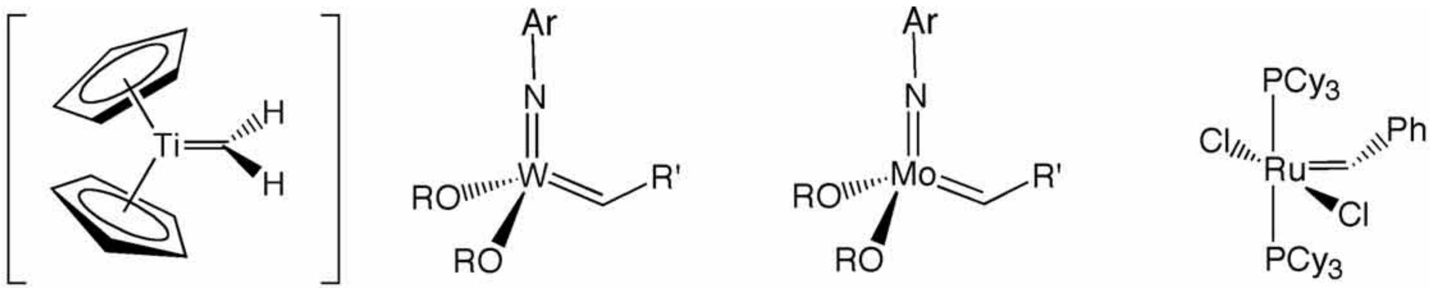
One Pot, 2 days, scales easily, > 15 kg in 50 gal reactor

Periodic Table of Elements

IA	IIA	IIIB	IVB	VB	VIB	VIIB	——	VII	——	IB	IB	IIIA	IVA	VA	VIA	VIIA	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											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 Br	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	106 106	107 107	108 108	109 109	110 110								

*Lanthinide Series	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	Lu Lu
*Actinide Series	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	Lr Lr

Metal-Centered-Functional Group



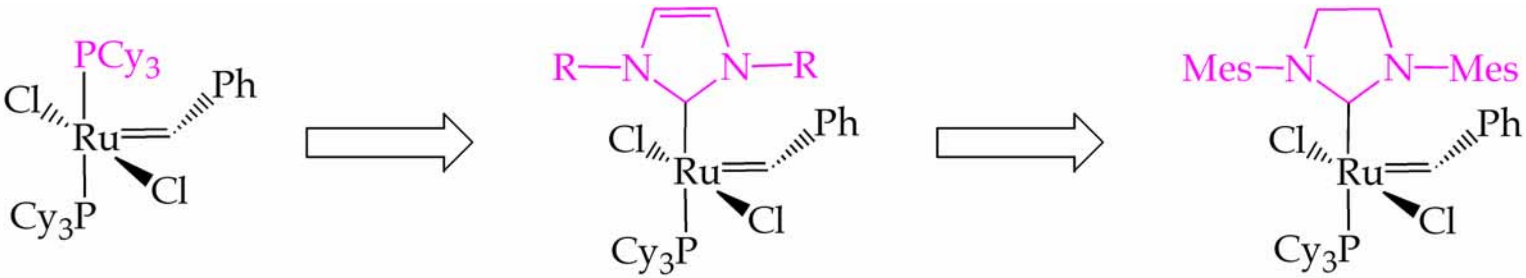
Titanium	Tungsten	Molybdenum	Ruthenium
Acids	Acids	Acids	**Olefins**
Alcohols, Water	Alcohols, Water	Alcohols, Water	Acids
Aldehydes	Aldehydes	Aldehydes	Alcohols, Water
Ketones	Ketones	**Olefins**	Aldehydes
Esters, Amides	**Olefins**	Ketones	Ketones
Olefins	Esters, Amides	Esters, Amides	Esters, Amides

Increasing order of reactivity ↑

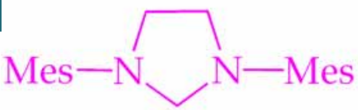
functional group tolerance →

← Activity

Catalyst Developments at Caltech



And Nolan and Herrmann



= H_2IMes

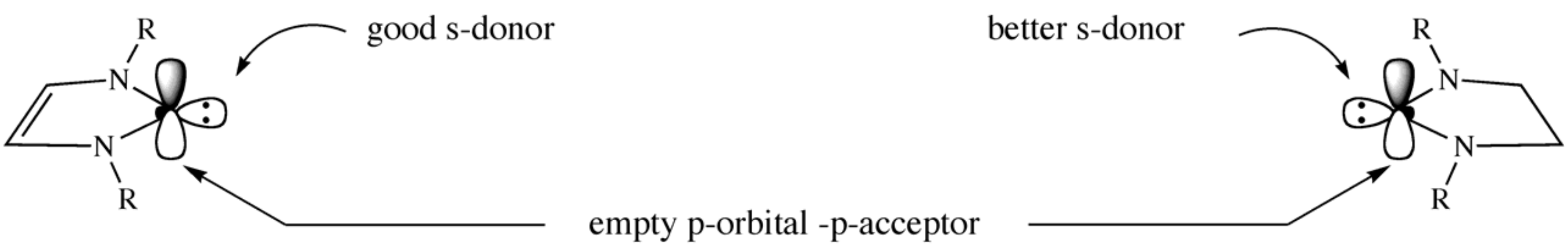
NHC catalysts are more active for RCM and ROMP (by 10^2-10^3)

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

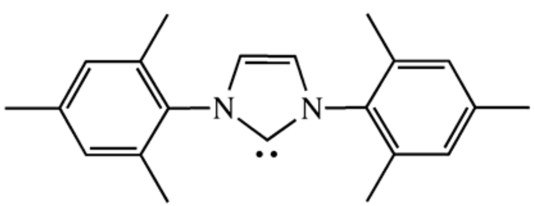
Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903.

N-Heterocycle Carbene Ligands

Singlet carbenes (as in N-Heterocyclic Carbenes)

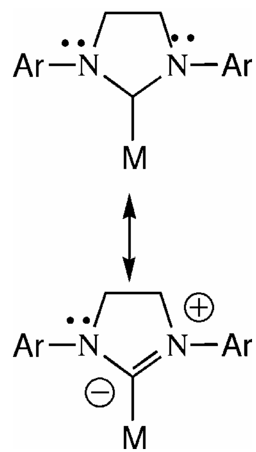


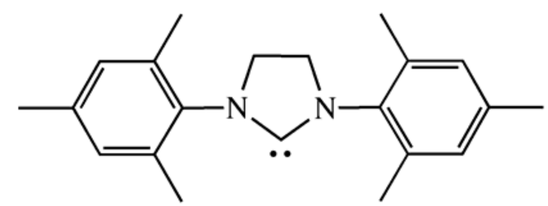
(although p-back-bonding from metal considered to be negligible)



IMes

1,3-dimesitylimidazol-2-ylidene

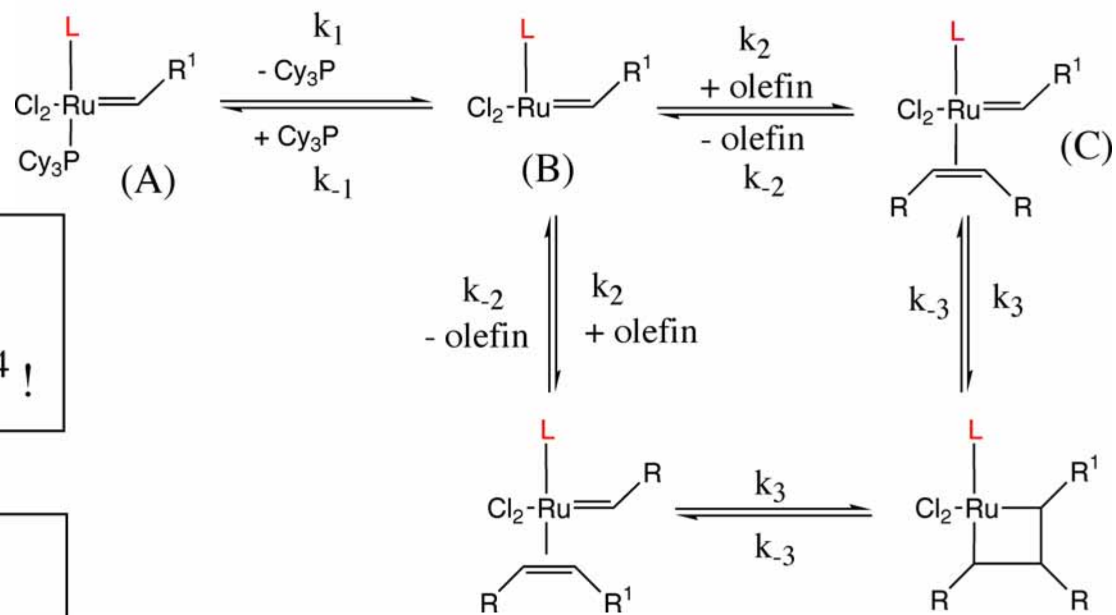




H_2IMes

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

Mechanism



$L = PCy_3$

k_1 (rel) = ~10^2

k_2/k_{-1} (rel)= ~10^{-4} !

$L = H_2IMes$

k_1 (rel) = 1

k_2/k_{-1} (rel)= 1

At steady state

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

k_{-1} [P] >> k_2 [=]

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

k_{-1} [P] << k_2 [=]

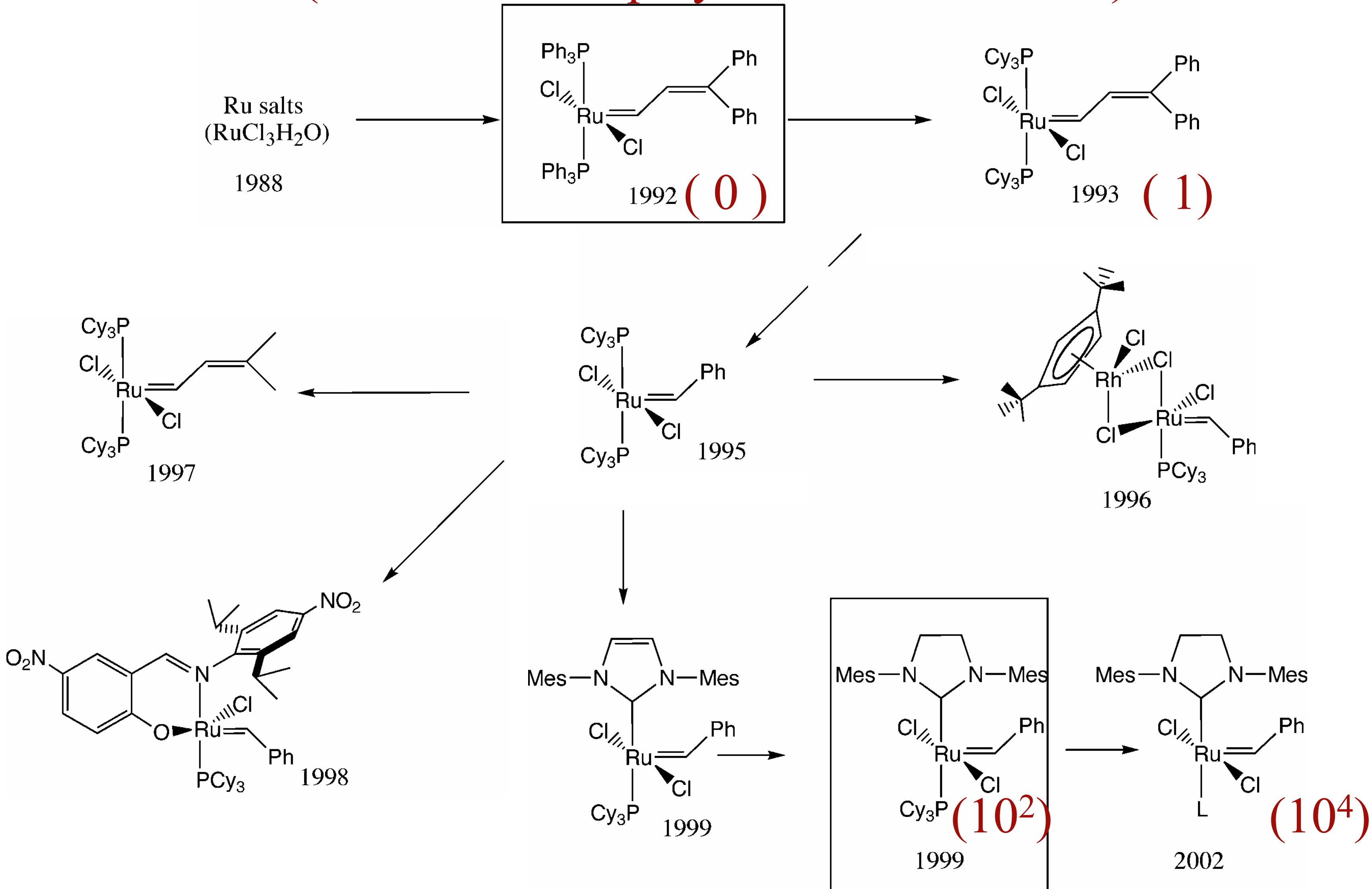
Saturation

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

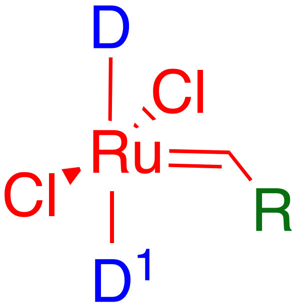
Eric Dias
Melanie Sanford
Jen Love

Ru Catalysis Evolution at Caltech

(relative rate of polymerization of COD)



Uses and Applications Resulting from Stable, Tolerant Catalysts

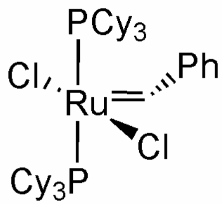


D=2 electron donor

General Catalyst Structure

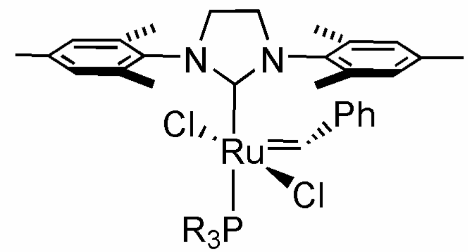
Commercial Ru Catalysts

First Generation

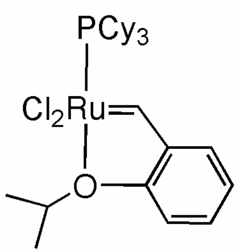


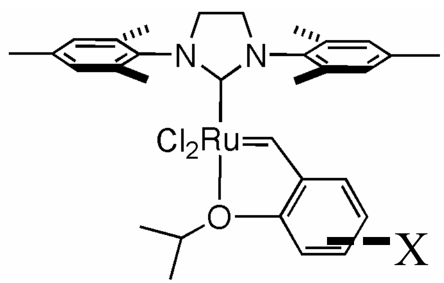
1. Kintically controled products (E:Z)
2. Selective for alkyl substuted double bonds

Second Generation



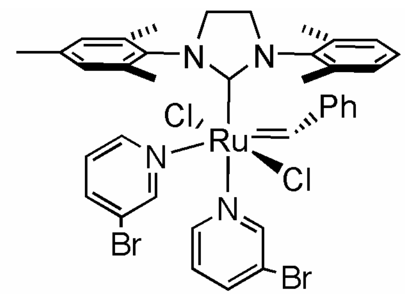
1. Thermodynamically Control of E:Z
2. Reacts with electron deficient double bonds





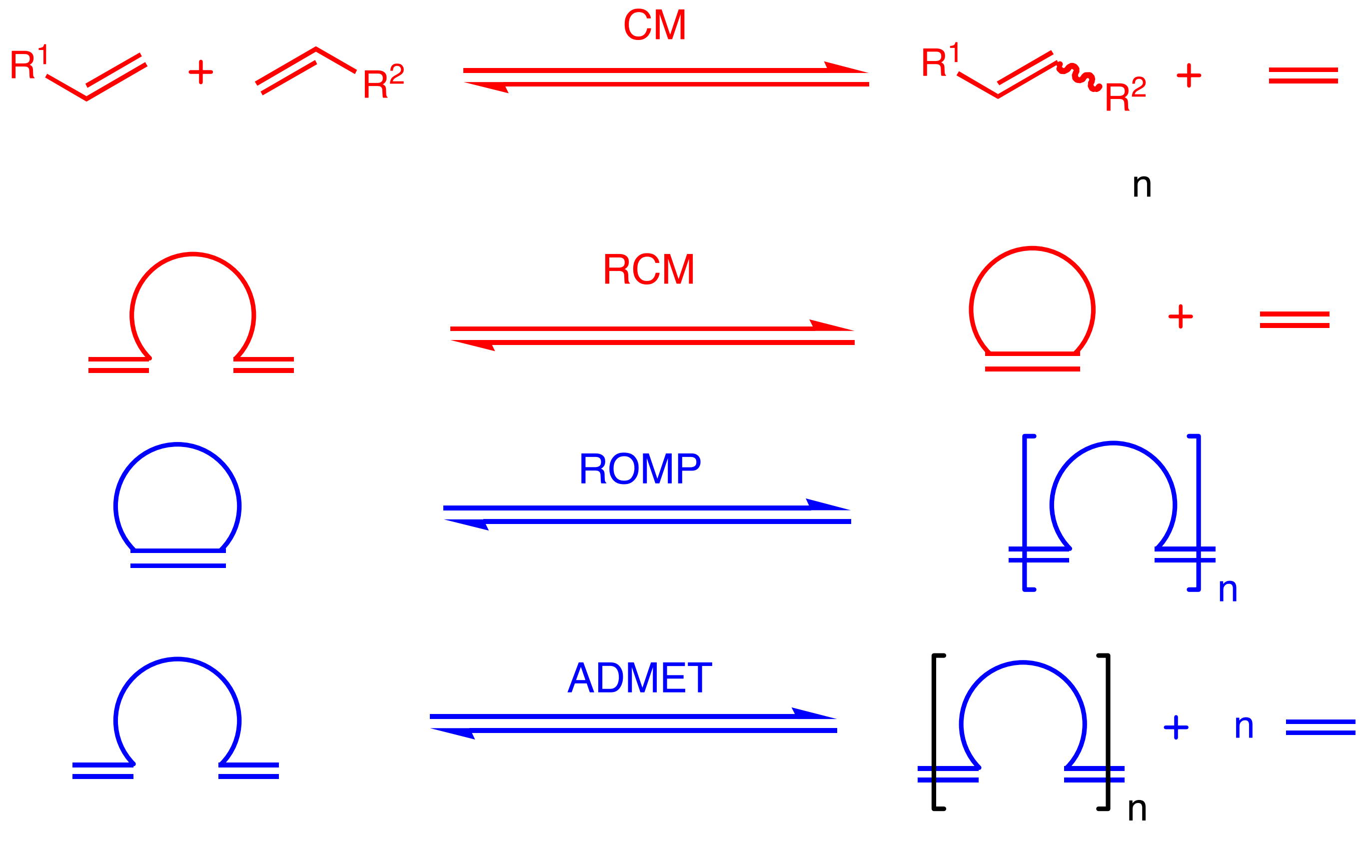
1. Slow initiation
2. Thermally more stable
3. Phosphine free

(Hoveyda)

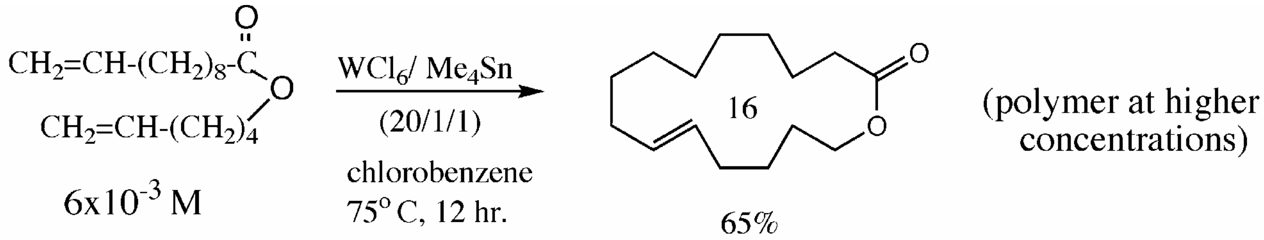


1. Rapid initiation
2. Less thermally stable

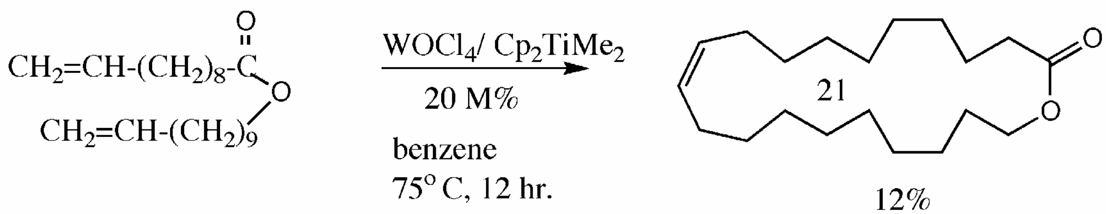
Carbon-Carbon Double Bond Forming Reactions



History of Ring Closing Metathesis



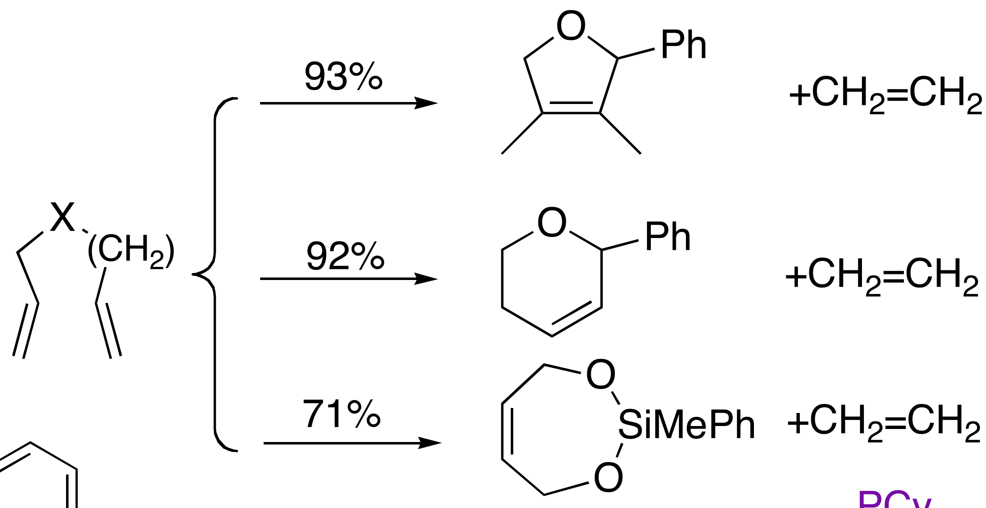
Didier Villemin, *Tetrahedron Letters*, **1980**, 1715

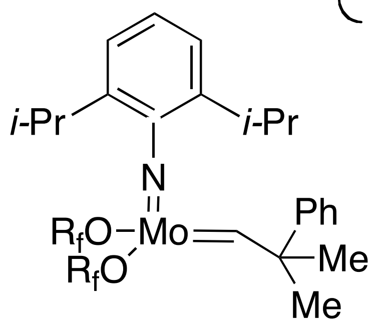


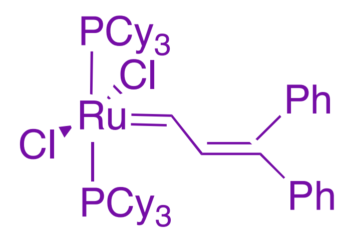
J. Tsuji and S Hashiguchi, *Tetrahedron Letters*, **1980**, 2955

"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





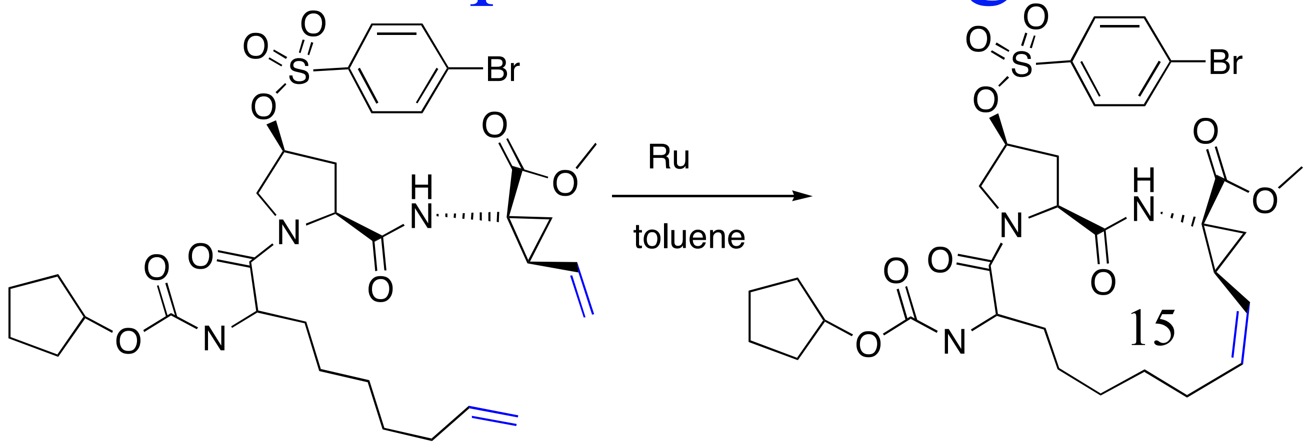


G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, **1992**, *114*, 5426-5427. *J. Am. Chem. Soc*. **1992**, *114 (18)*, 7324-7325. , *J. Am. Chem. Soc.*, **1993,** *115*, 3800-3801

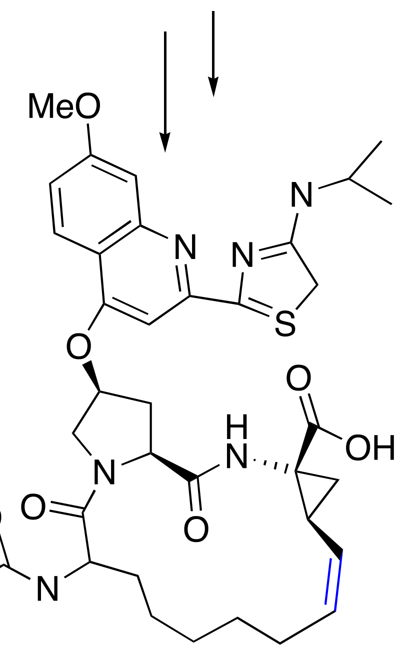
G. C. Fu, S. T. Nguyen, and R. H. Grubbs, *J. Am. Chem. Soc*. **1993**, *115*, 9856-9857

Pharmaceutical Applications

Boehringer Ingelheim
Hepatitis C Drugs



400 kg.



HCV Serine Protease Inhibitor

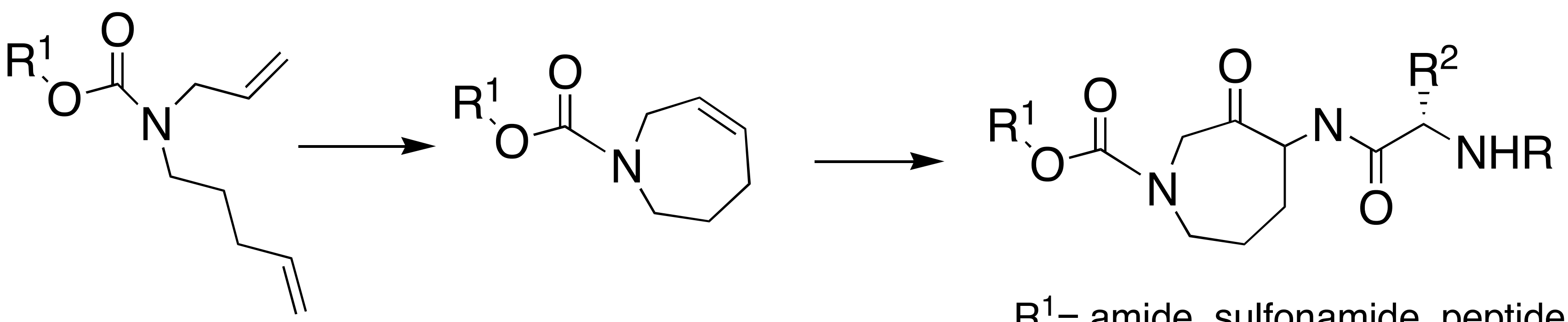
Boehringer Ingelheim's BILN 2061

Phase II Clinical Trials in US and Europe

T. Nicola, M. Brenner, K. Donsbach, and P. Kreye,

Organic Process and Development, **2005,** 27.

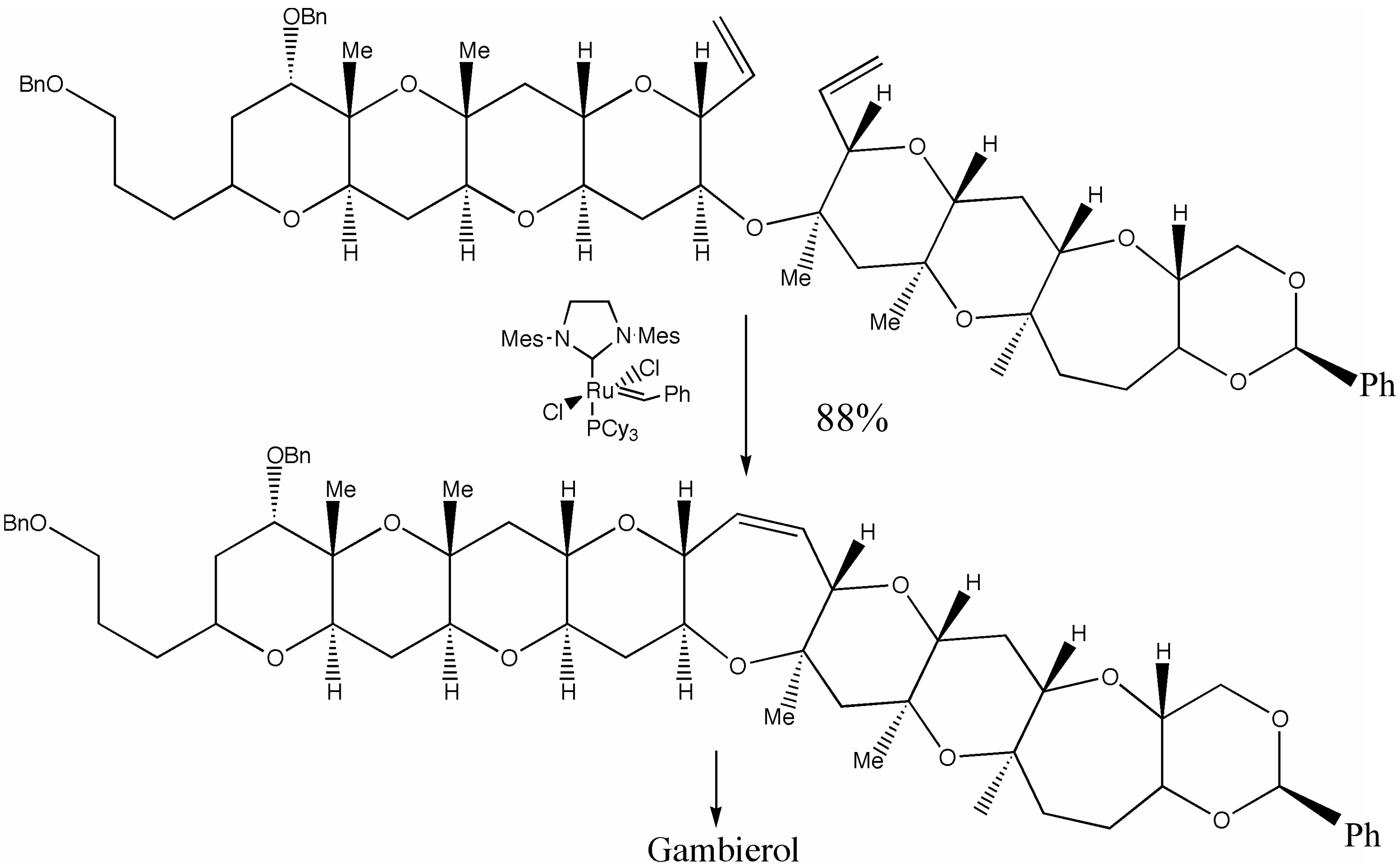
GSK Osteoporosis Drug



R^1= amide, sulfonamide, peptide
R^2 = aminoacid side chain

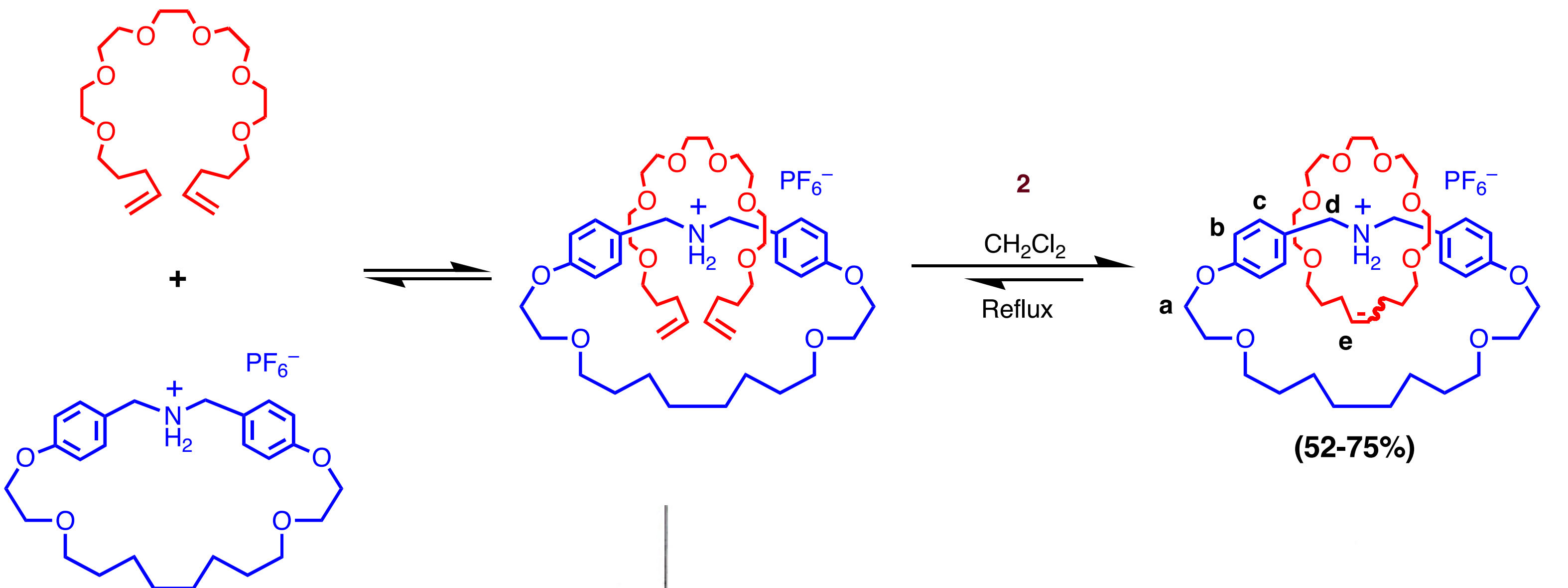
Protease Inhibitor of cathepsin K

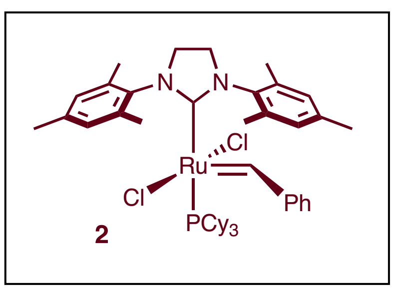
Synthesis of a Large Natural Product

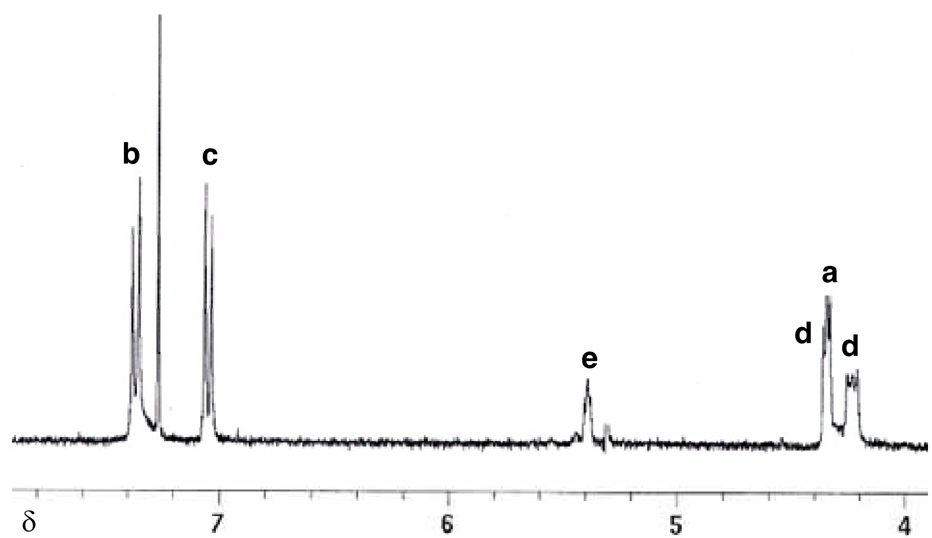


I. Kadota, H. Takamura, K. Sato, A. Ohno, K. Matusuda, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 46-47

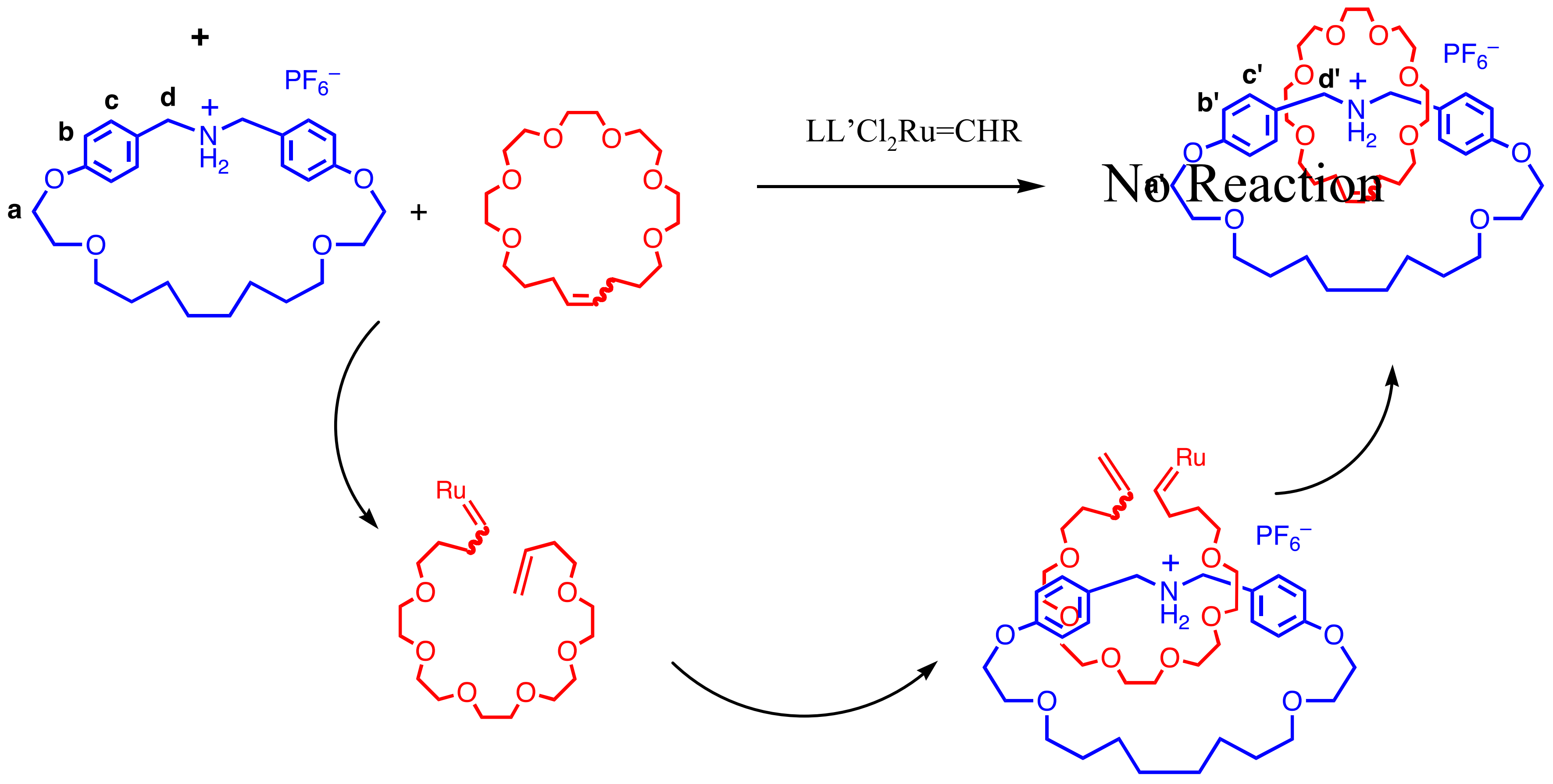
Catenane Formation



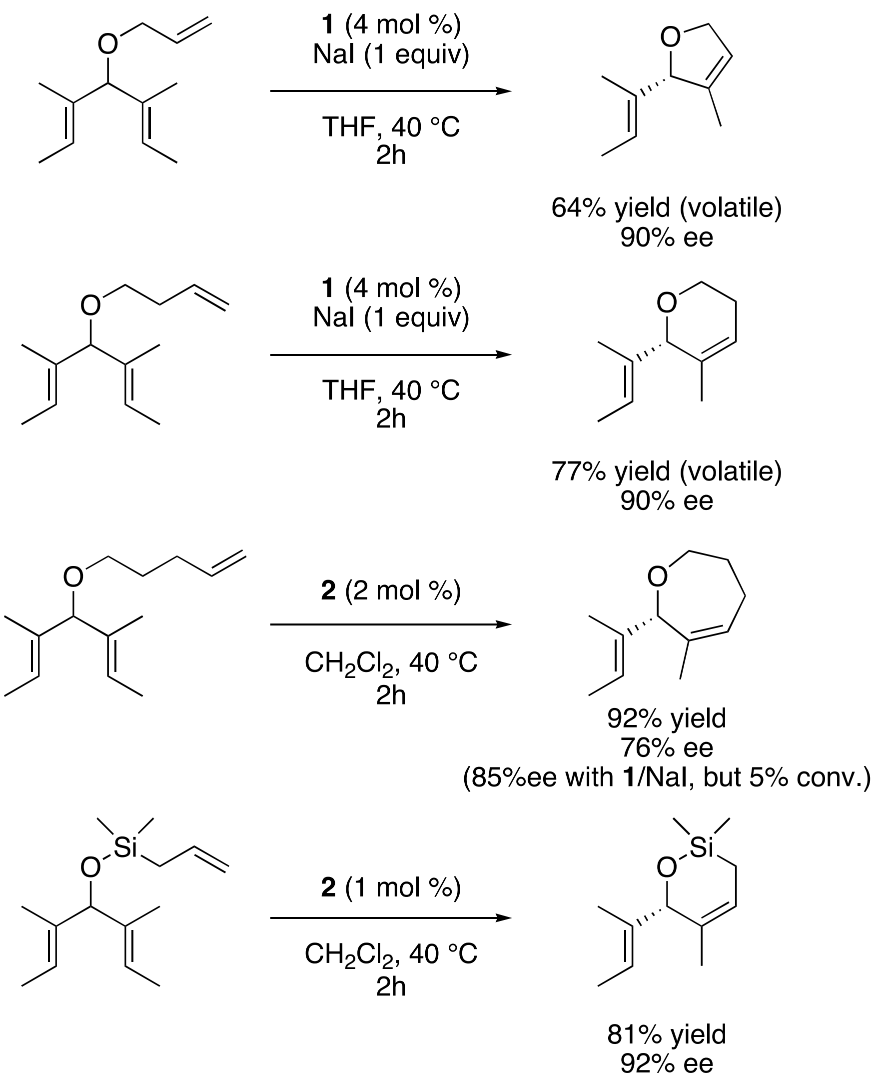


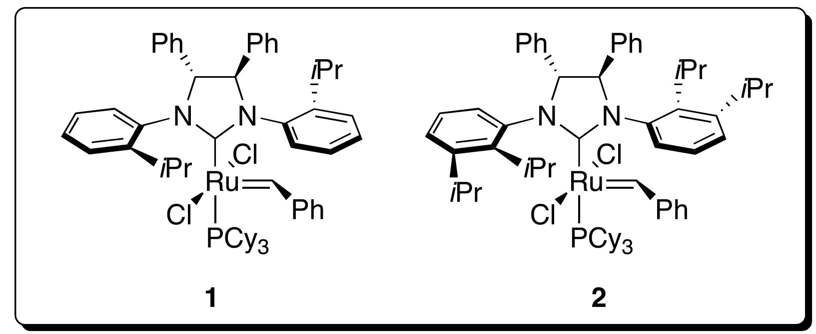


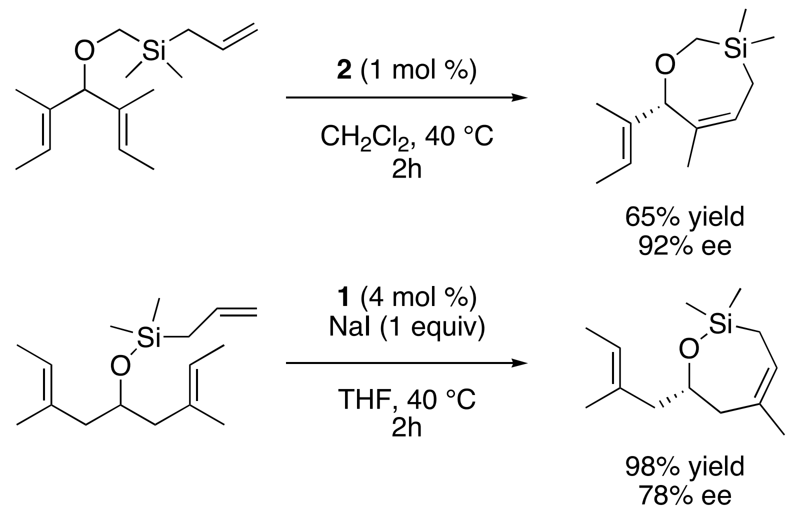
Magic Rings



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

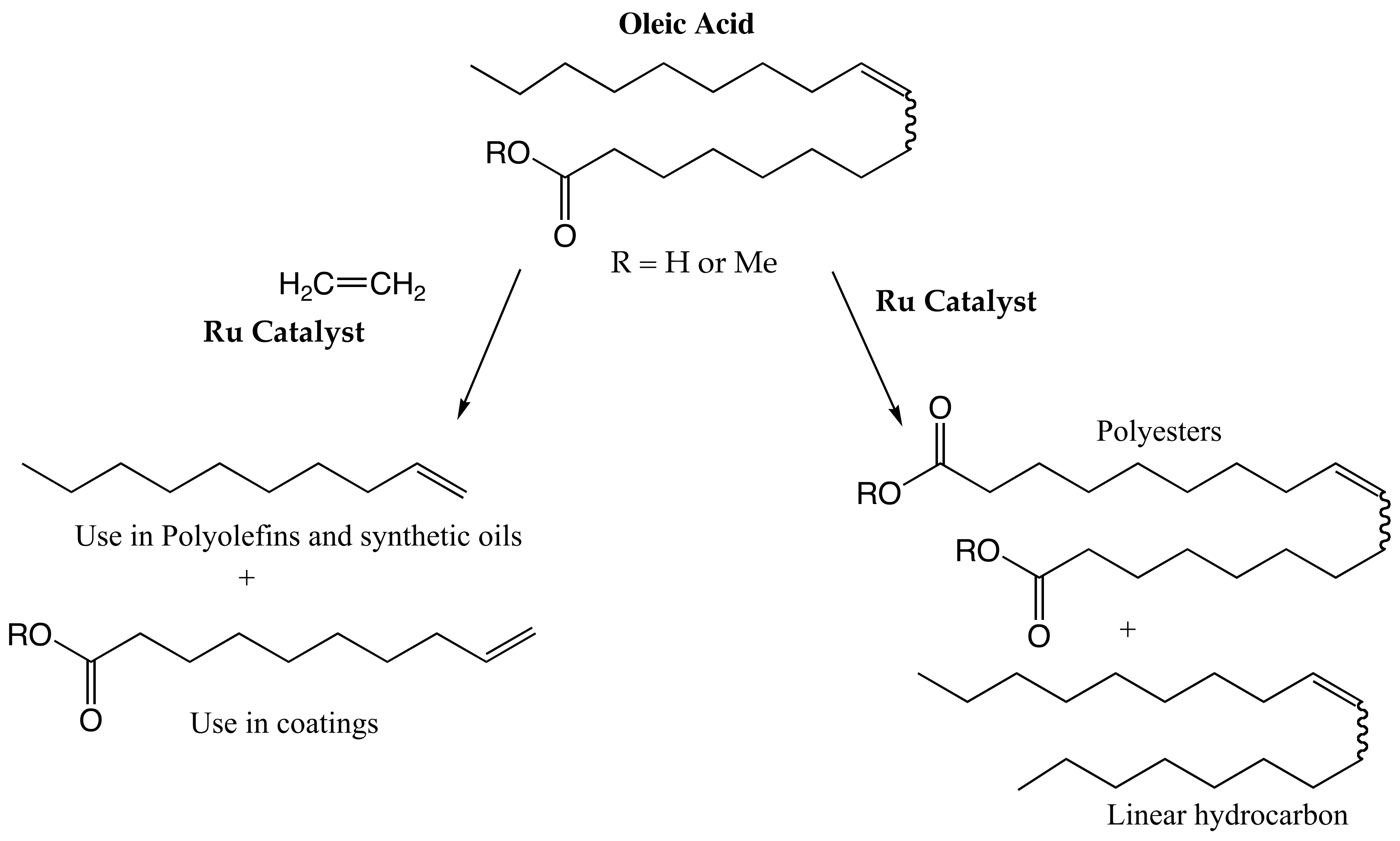
Cargill- Materia- Caltech-DOE

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

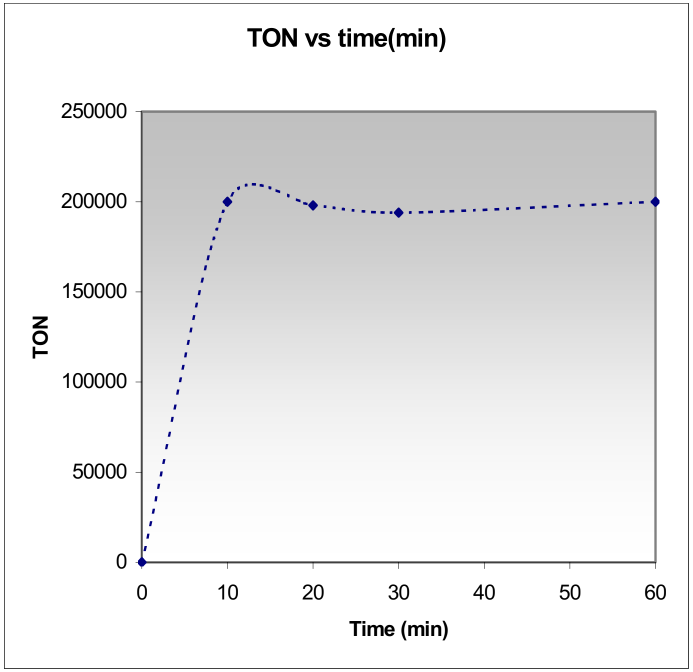
Cargill anticipates that it will have commercial sales in 2006 of several million pounds of a proprietary Ruthenium-metathesis based product derived from a renewable resource that will replace a petroleum-based material.

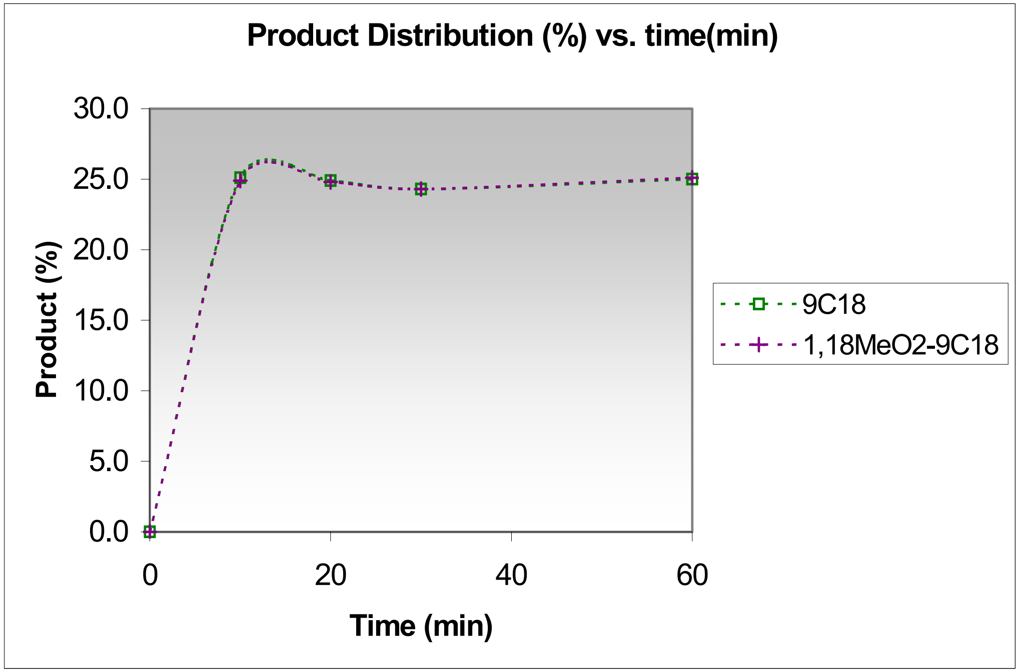
Oleic Acid to Value Added Chemicals



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

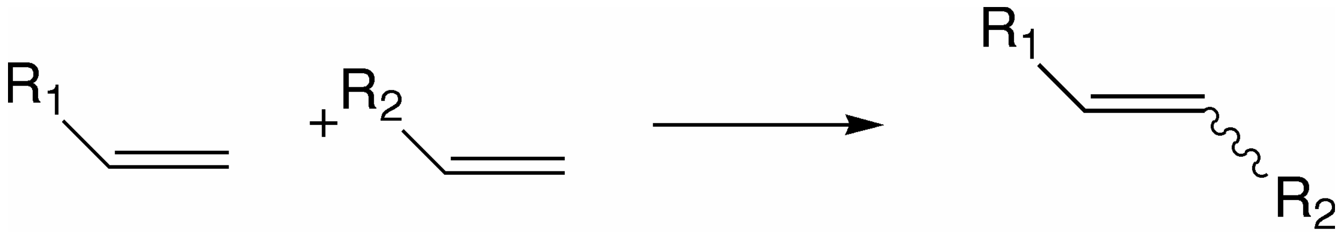
Sample #	Time (min)	MO (%)	$9C_{18}$ (%)	$1,18MeO_2\text{-}9C_{18}$ (%)	Impurities (%)	SM (%)	TON
0	0	100.0	0.0	0.0	0.0	0	0
067-007-1-10	10	49.9	25.1	24.9	0.1	100	200000
067-007-1-20	20	50.3	24.9	24.8	0.0	99	198000
067-007-1-30	30	51.4	24.3	24.3	0.0	97	194000
067-007-1-60	60	49.9	25.0	25.1	0.0	100	200000





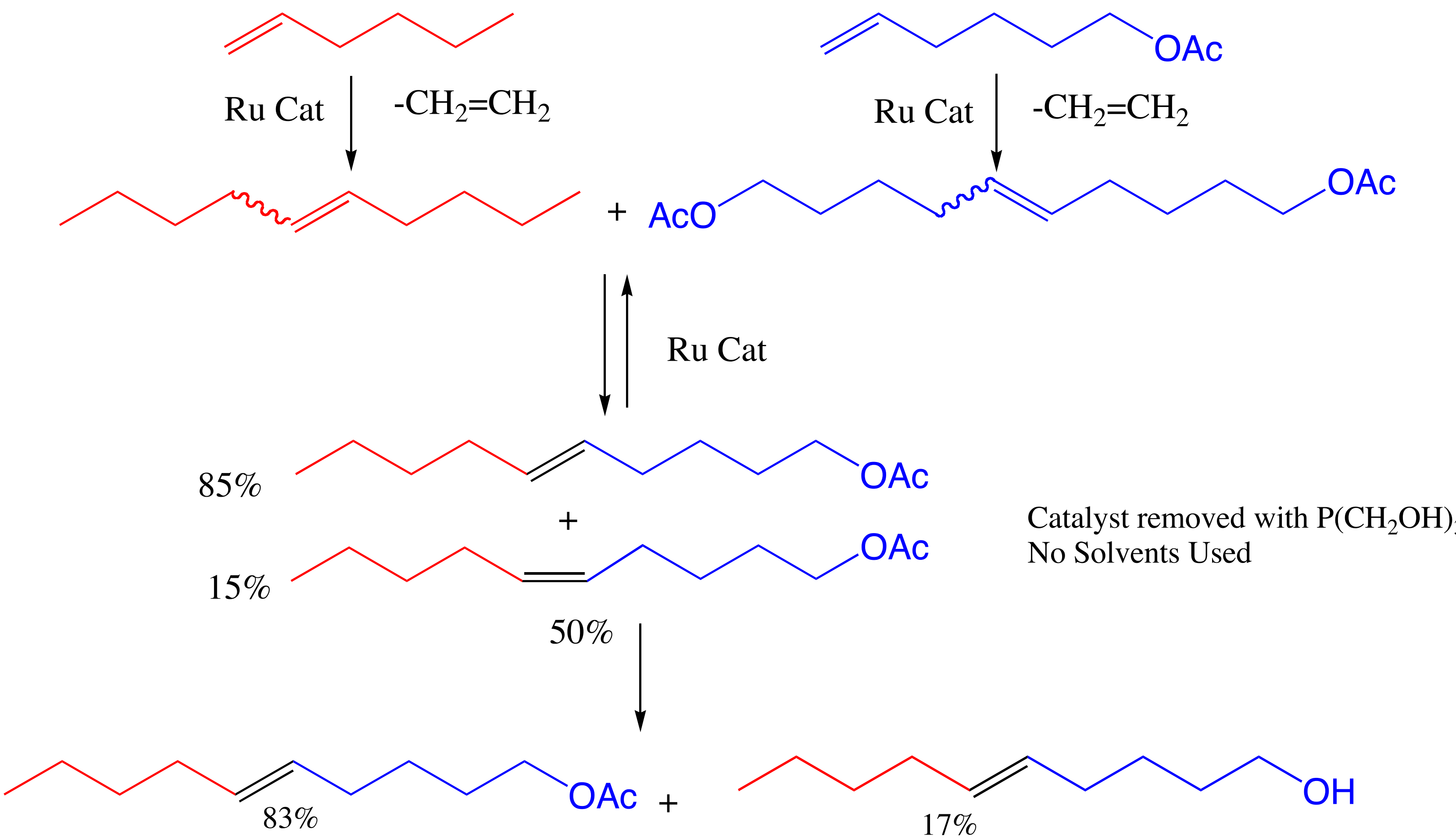
TON = 200,000; TOF = 1,200,000 h^{-1}; extremely low impurity formation

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%

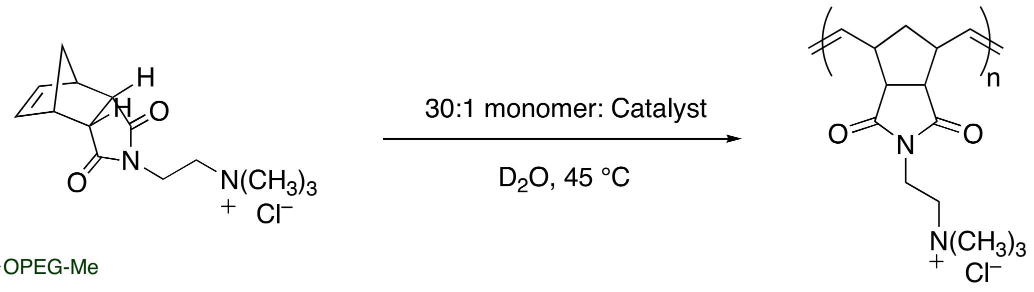
Pheromone by Cross Metathesis

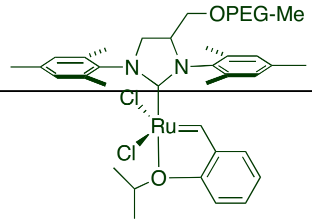


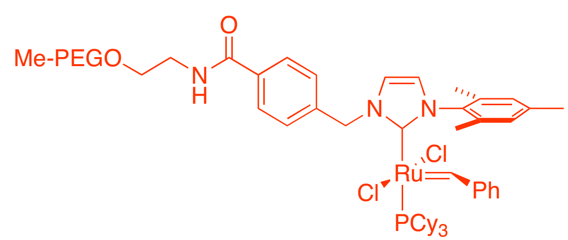
PHEROMONE for Peach Twig Borer
Used in Mating Disruption

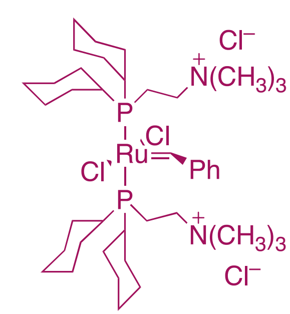
Water as a Solvent

ROMP of Water-Soluble Endo-Monomer

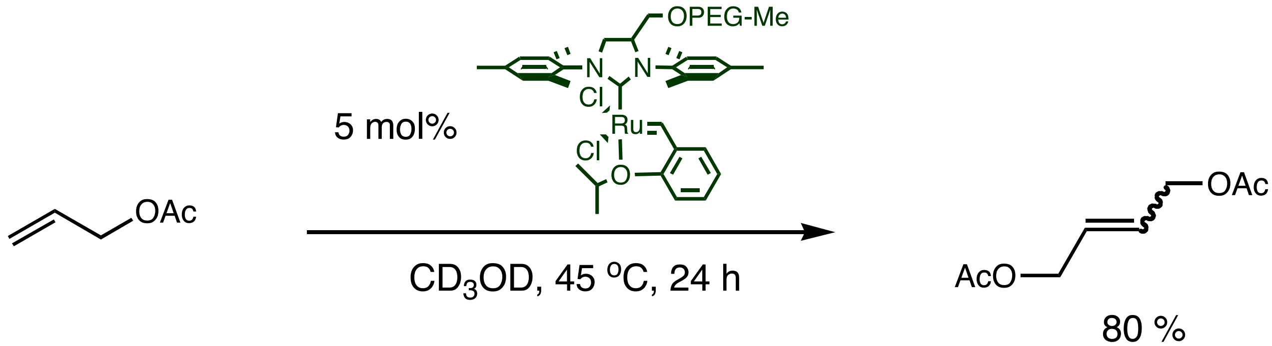


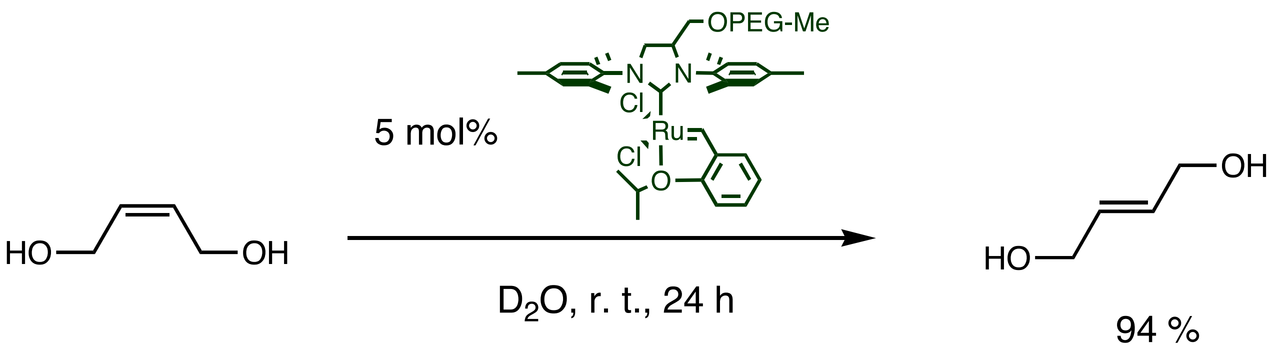


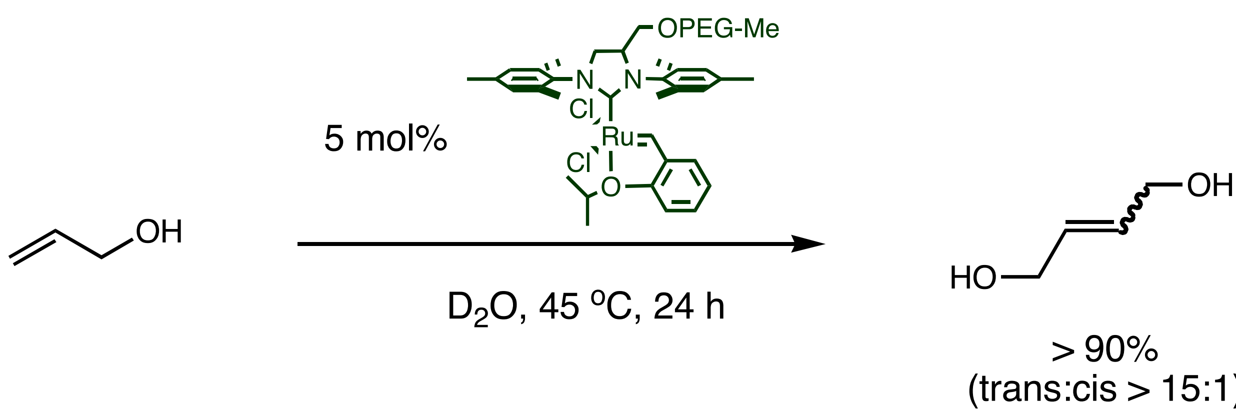




Cross Metathesis





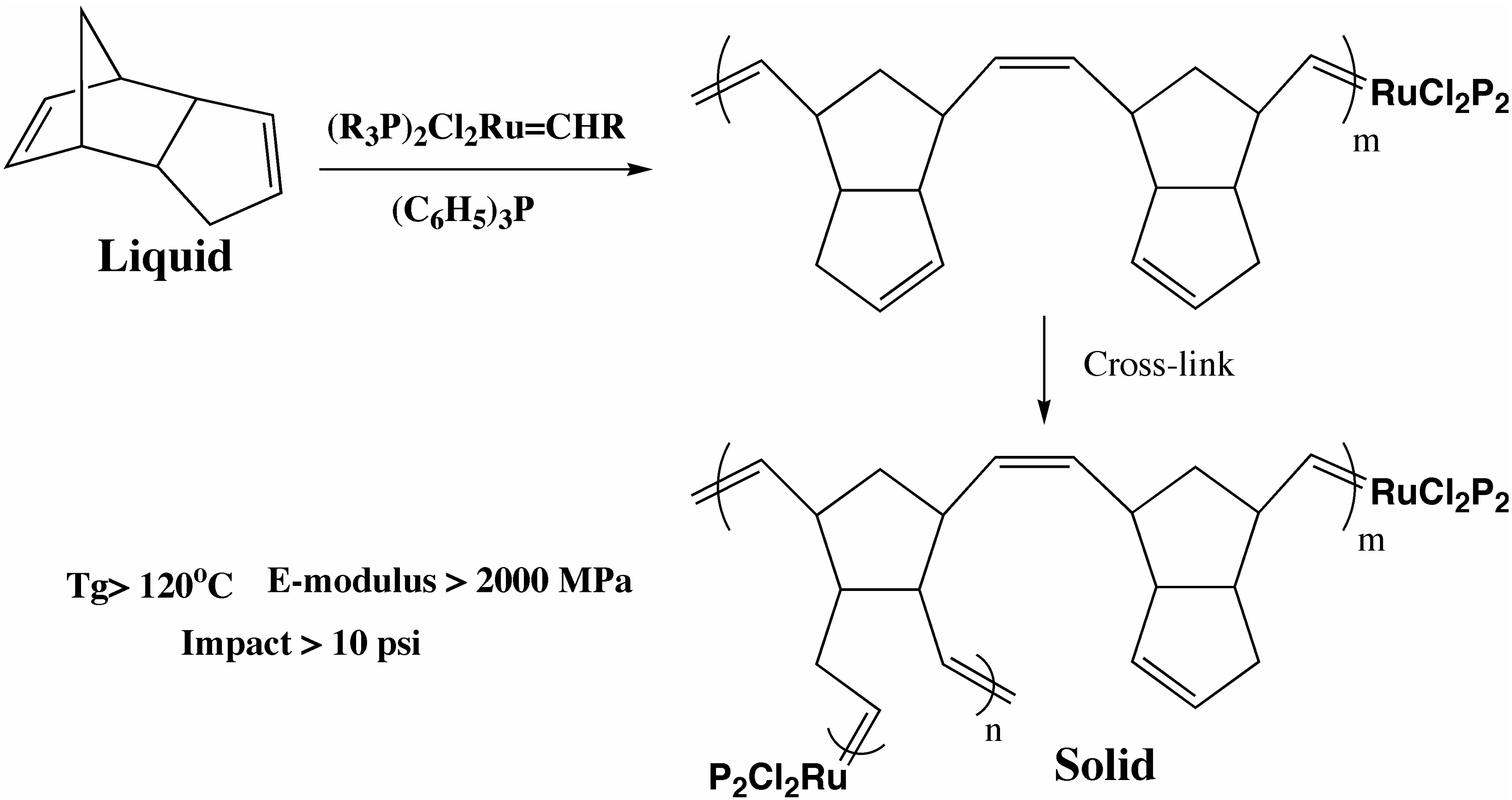


Polymer Synthesis

Mechanical Properties

Chemical Function

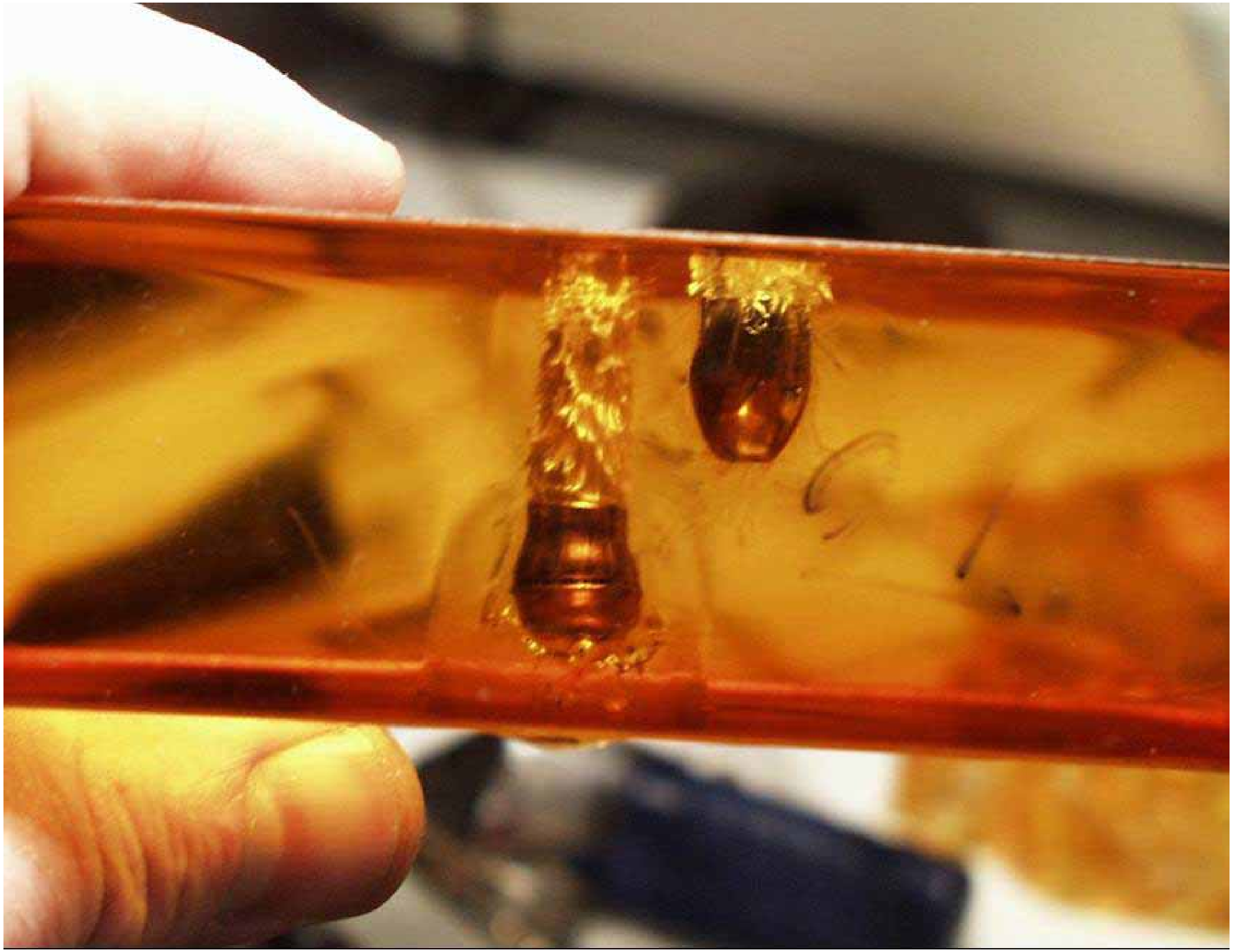
Dicyclopentadiene-Thermoset Polymer



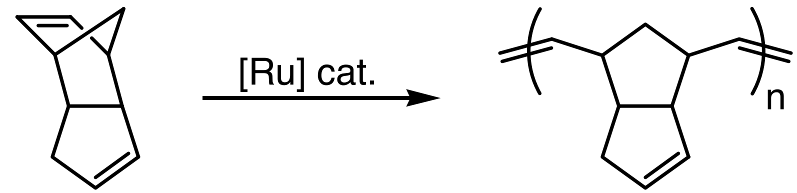
Tg> 120°C E-modulus > 2000 MPa

Impact > 10 psi

PolyDCPD-9mm Ballistic Protection



Products Made With DCPD ROMP



DCPD poly(DCPD)

Consumer products

Sports Equipment

Truck Parts

www.plastictechnology.com
baseball.eastonsports.com

Acknowledgements

- All my Professors and others who have provided inspiration on my journey from the American equivalent of Åmål.
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