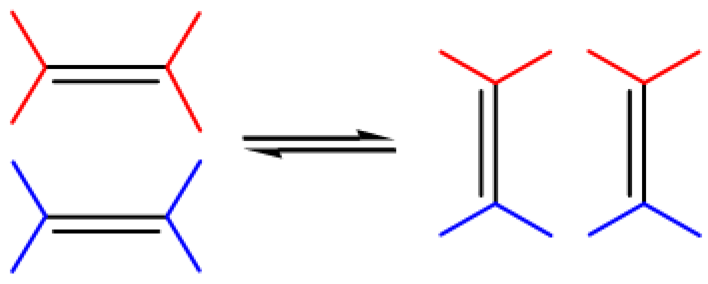
Olefin metathesis



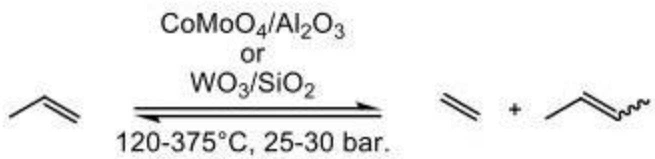
Olefin metathesis (or transalkylidenation) is an organic reaction that entails redistribution of alkylene fragments by the scission of carbon - carbon double bonds in alkenes.

Table of contents

I. History

Industry: The Origin of Metathesis

Phillips' Triolefin Process (1964)



• First plant in Montreal from 1966-1972

Mol, J. C. *J. Mol. Cat. A* **2004**, *213*, 49.
Banks, R. L.; Bailey, G. C. *Ind. Eng. Chem., Prod. Res. Dev.* **1964**, 170.

Nobel Prize in Chemistry 2005

Yves Chauvin

Richard R. Schrock

Robert H. Grubbs

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

The contribution of Yves Chauvin

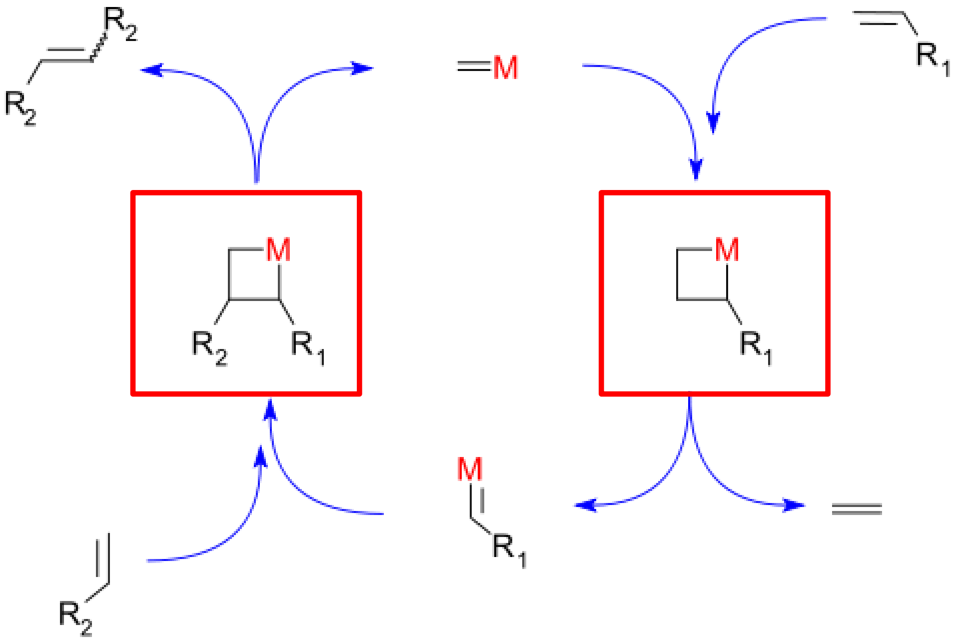
Yves Chauvin

….the mechanism….

The contribution of Yves Chauvin

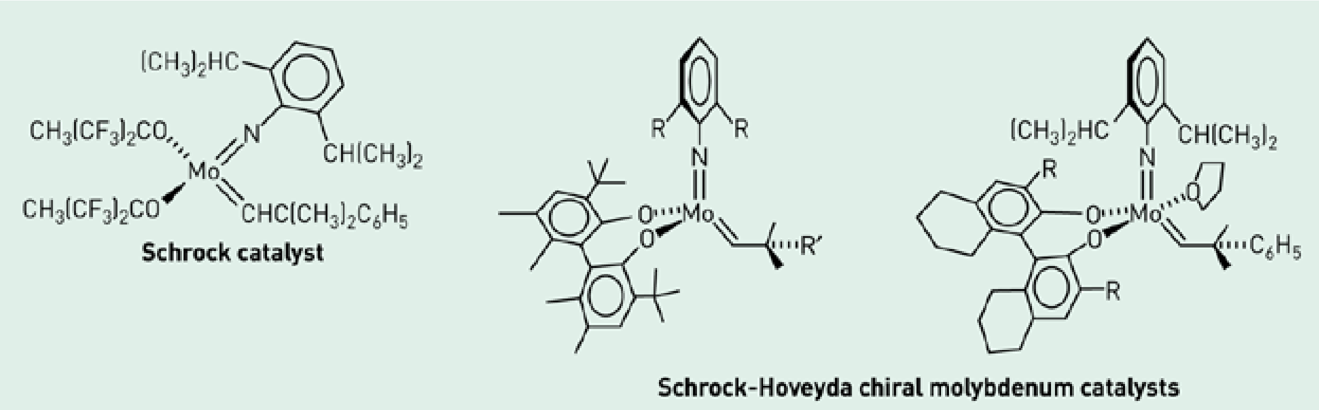
Yves Chauvin

….the mechanism….



The contribution of Richard Schrock

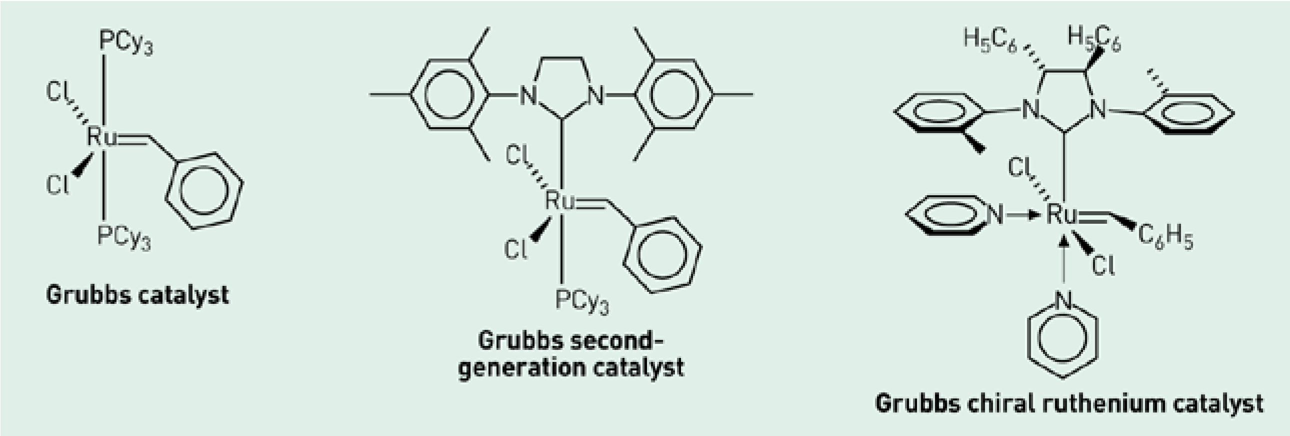
Richard R. Schrock



….Molybdenum metathesis catalysts (very active but air sensitive)….

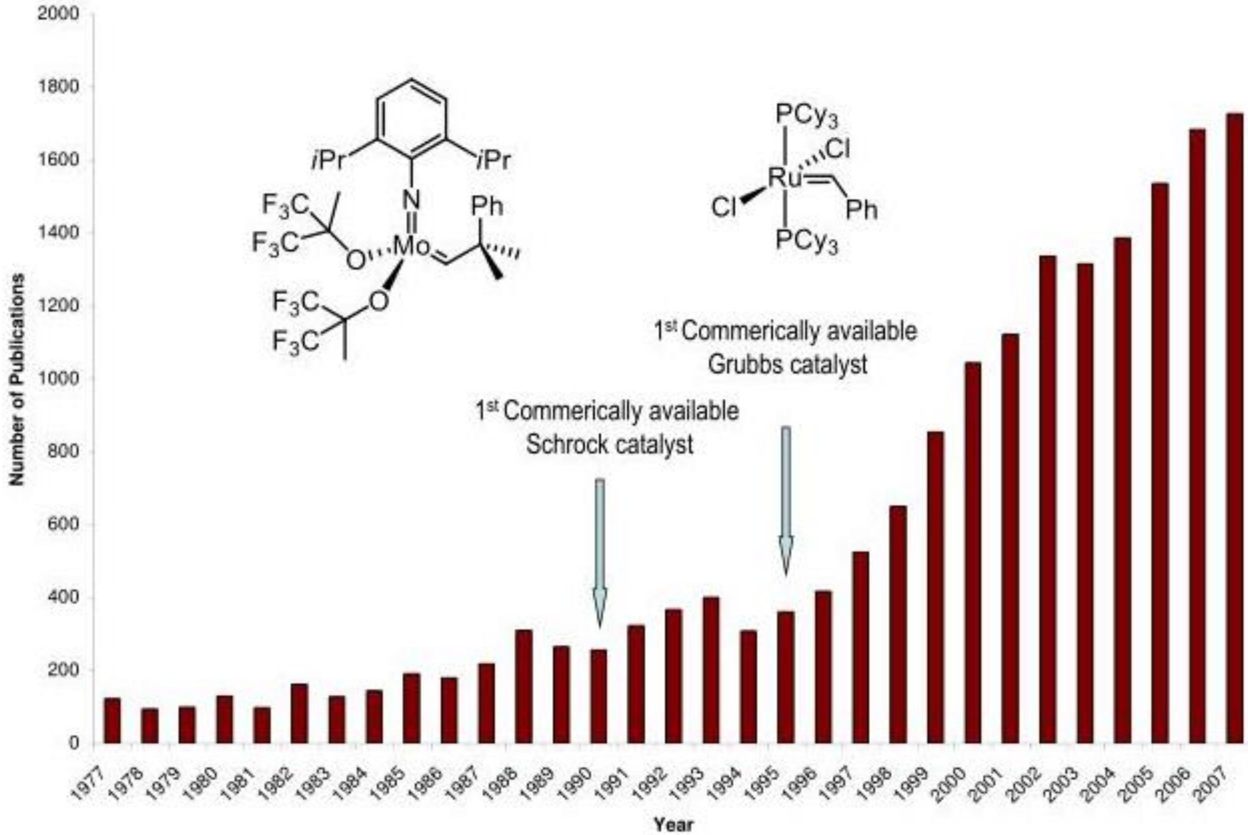
The contribution of Robert Grubbs

Robert H. Grubbs

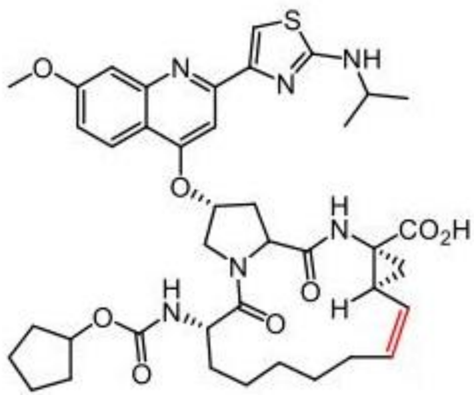


….Ruthenium metathesis catalysts (stable)….

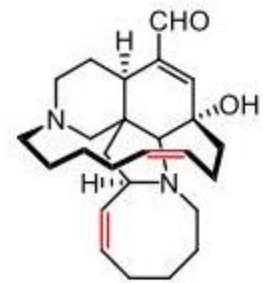
Metathesis Publications



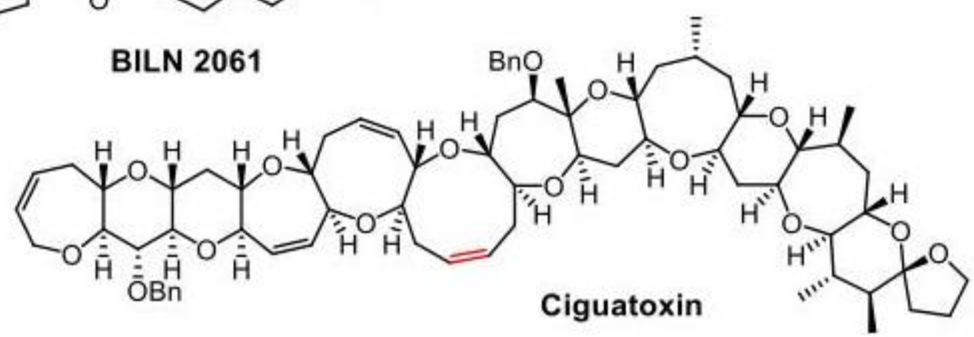
Metathesis in Synthesis



BILN 2061



Ircinal A



Ciguatoxin

Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904.
Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866.
Faucher, A.-M. *Org. Lett.* **2004**, *6*, 2901.

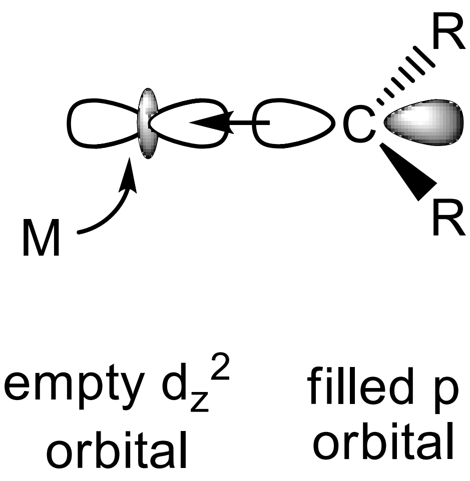
II. Electronic structure of catalysts

Carbenes

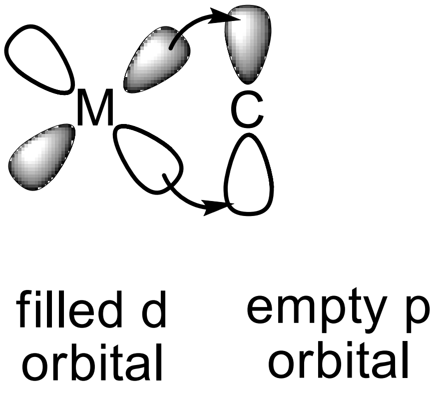
Both the Schrock and Grubbs cataylsts contain metal-carbene (M=C) bonds.

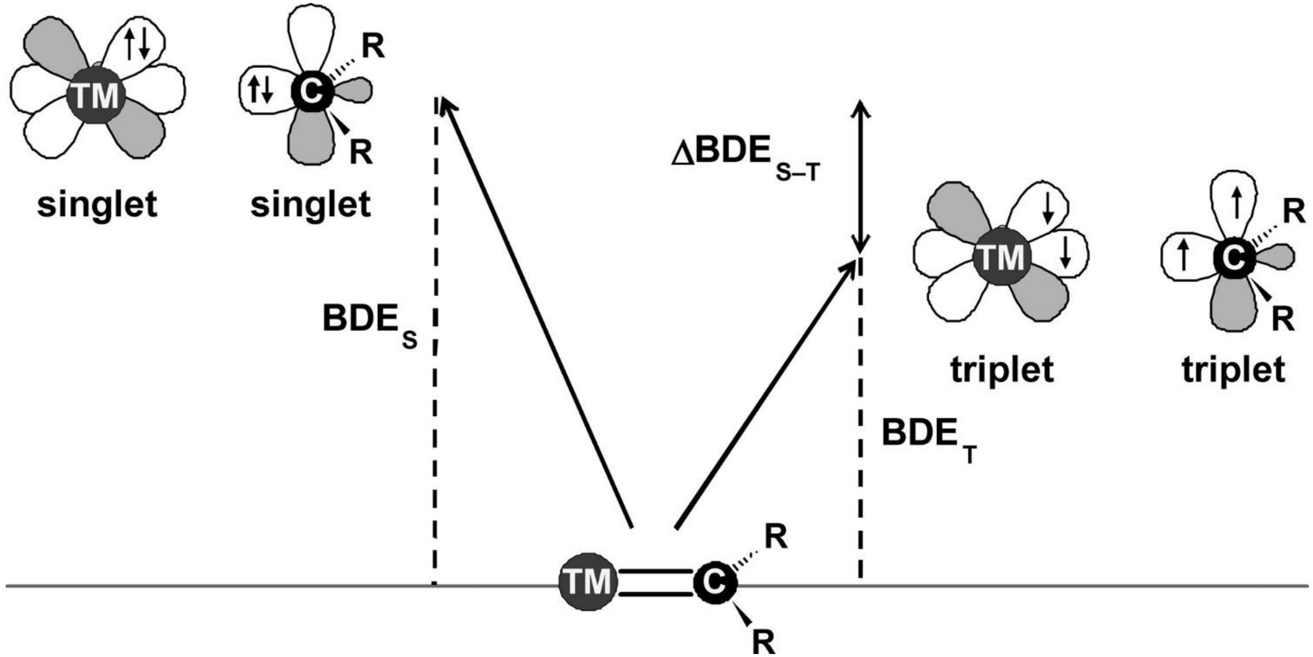
Bonding in carbenes:

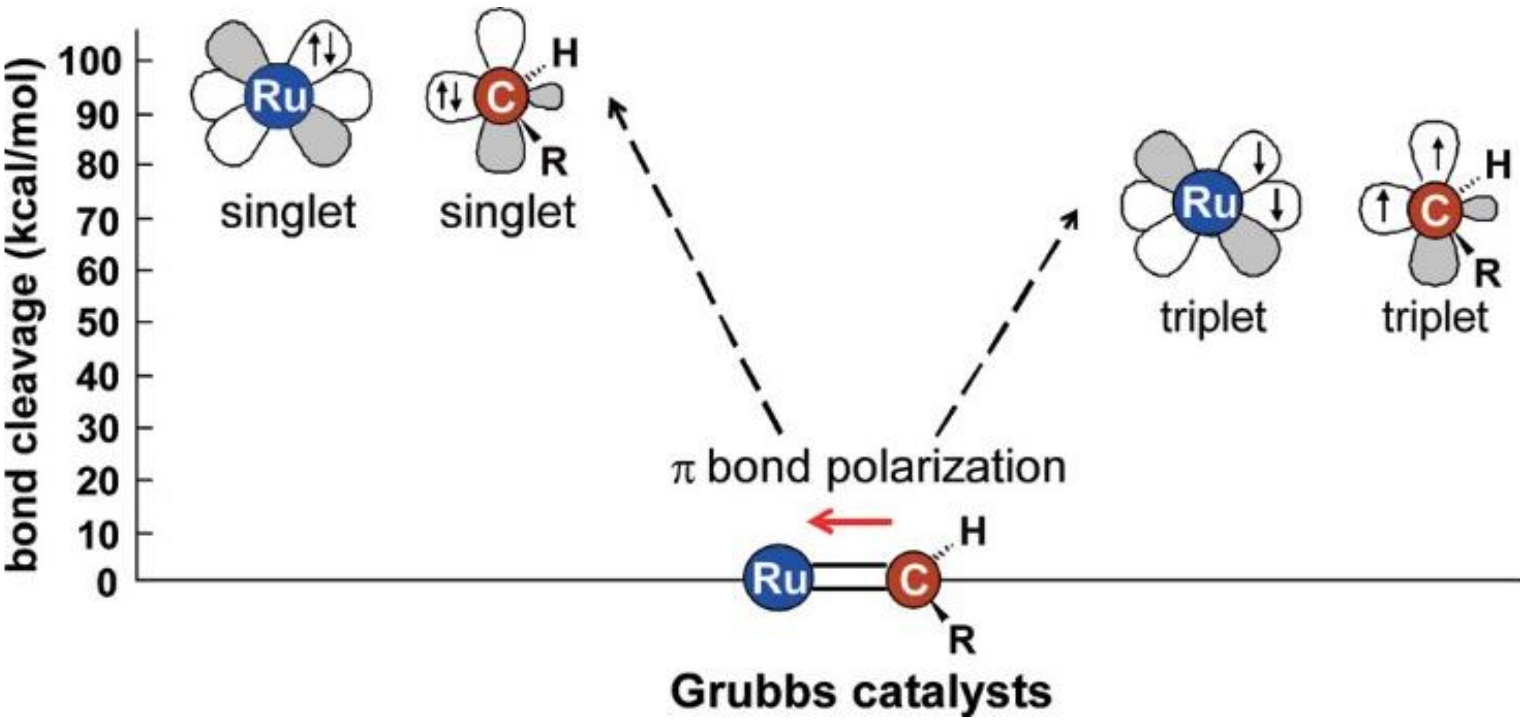
σ-bonding



π-bonding



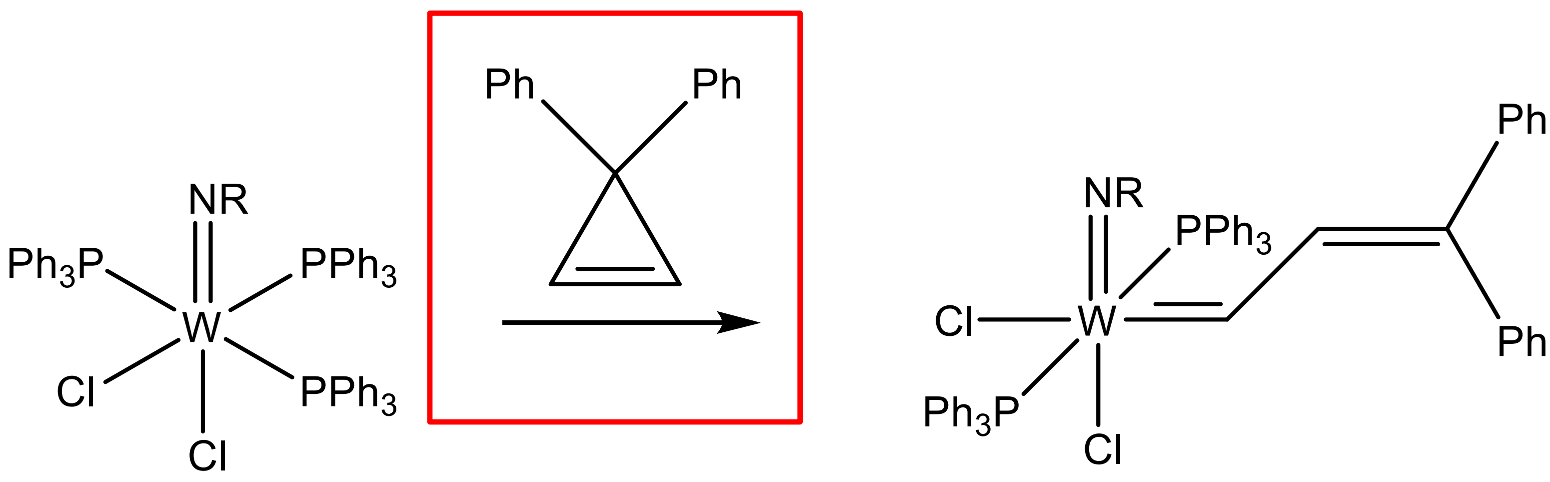

singlet
singlet
R
R
TM
C
BDE_S
ΔBDE_S–T
BDE_T
triplet
triplet
TM
C
R
R



Here Ru is more π-electronegative than C, making C electrophilic
If it is Mo, then Mo is less π-electronegative than C, making C nucleophilic

Synthesis of carbene complexes

3,3-diphenylcyclopropene is a useful reagent for the synthesis of metal-carbene complexes.

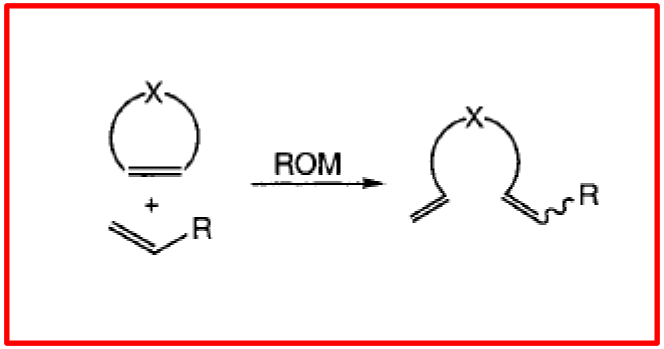


Exercise: Draw a mechanism for this reaction

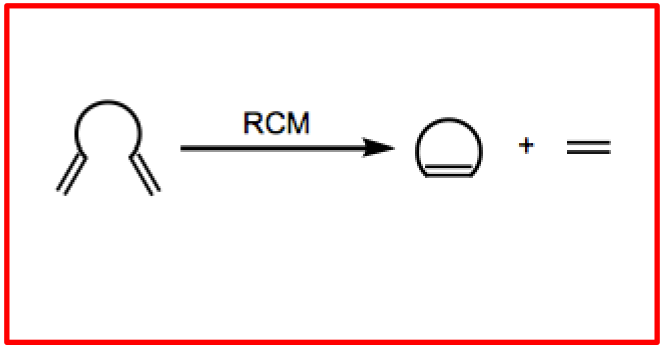
III. Synthetic applications – ROMP and RCM

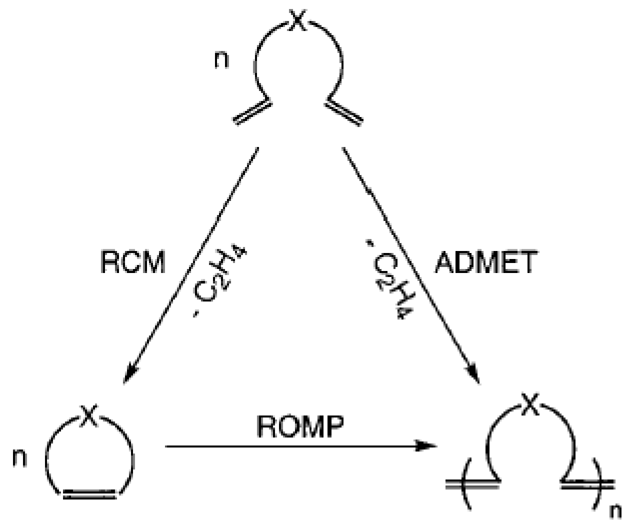
A Versatile Method for Synthetic Chemistry

Ring opening metathesis



Ring closing metathesis



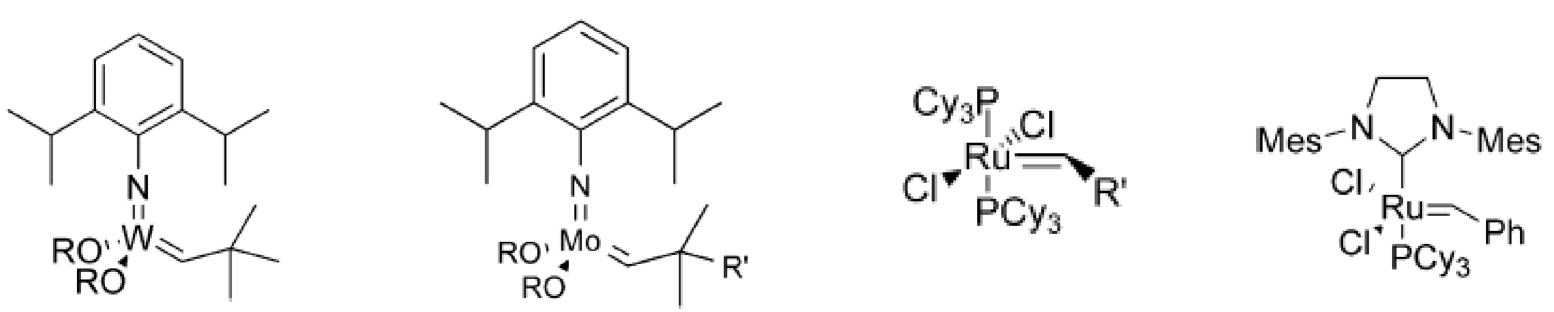


Also ring opening polymerisation methathesis (ROMP) and acyclic diene metathesis polymerisation (ADMET)

Ring Opening Metathesis Polymerization (ROMP)

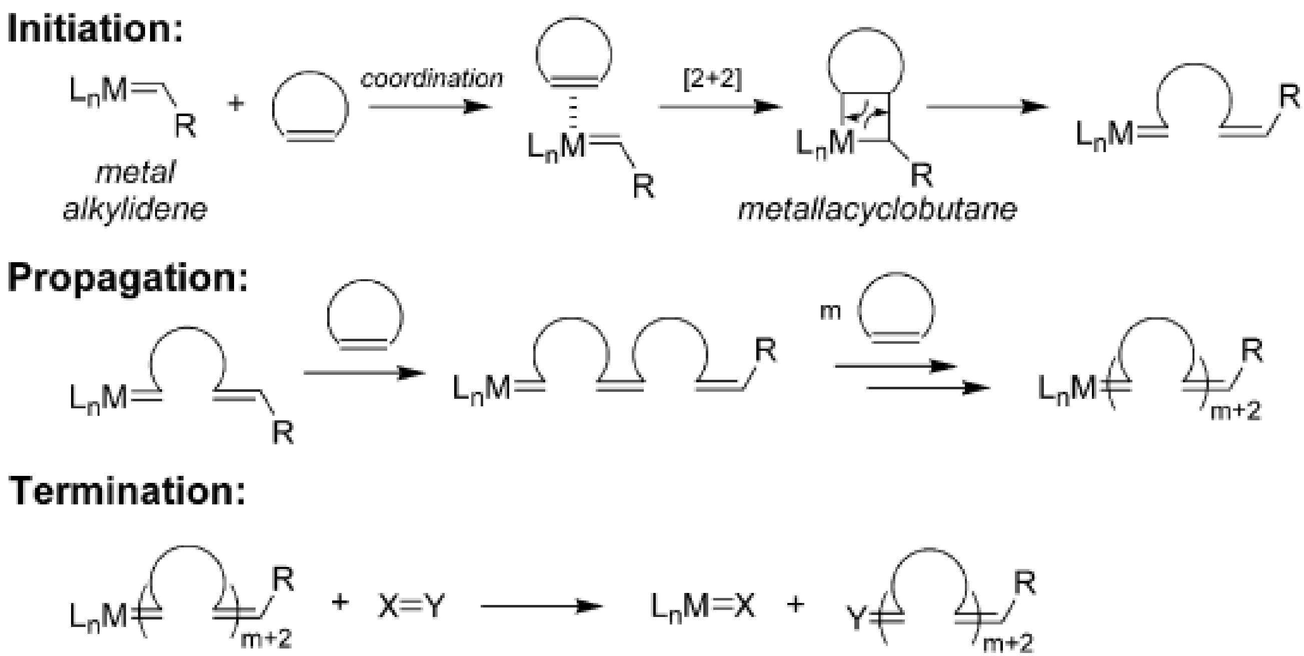
- Mechanism:

- Catalysts: titanium, tantalum, tungsten, molybdenum, ruthenium

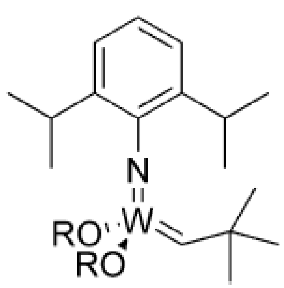


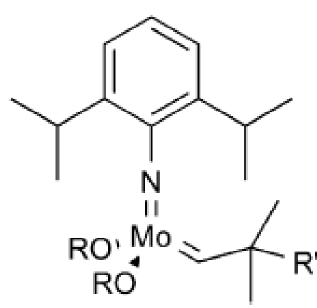
Ring Opening Metathesis Polymerization (ROMP)

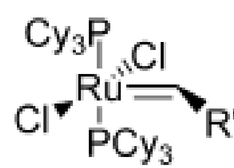
- Mechanism:

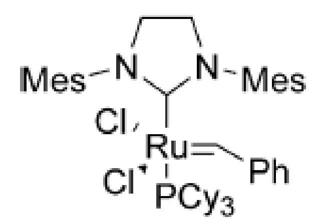


- Catalysts: titanium, tantalum, tungsten, molybdenum, ruthenium



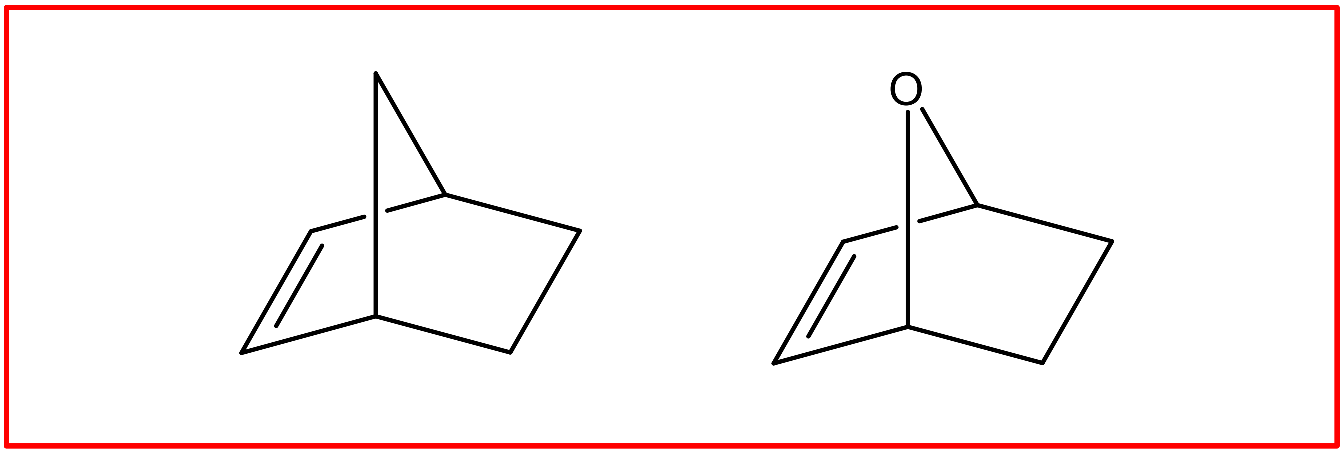


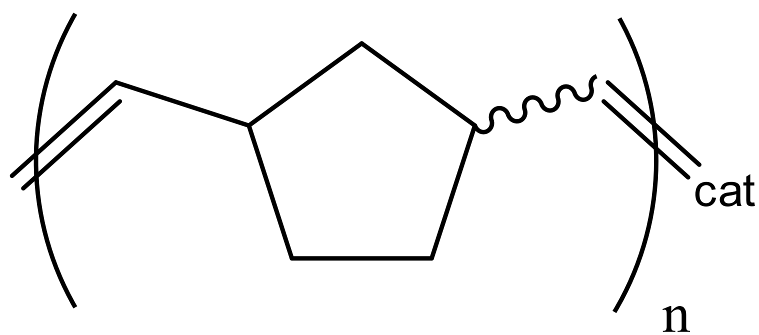




Ring Opening Metathesis Polymerisation

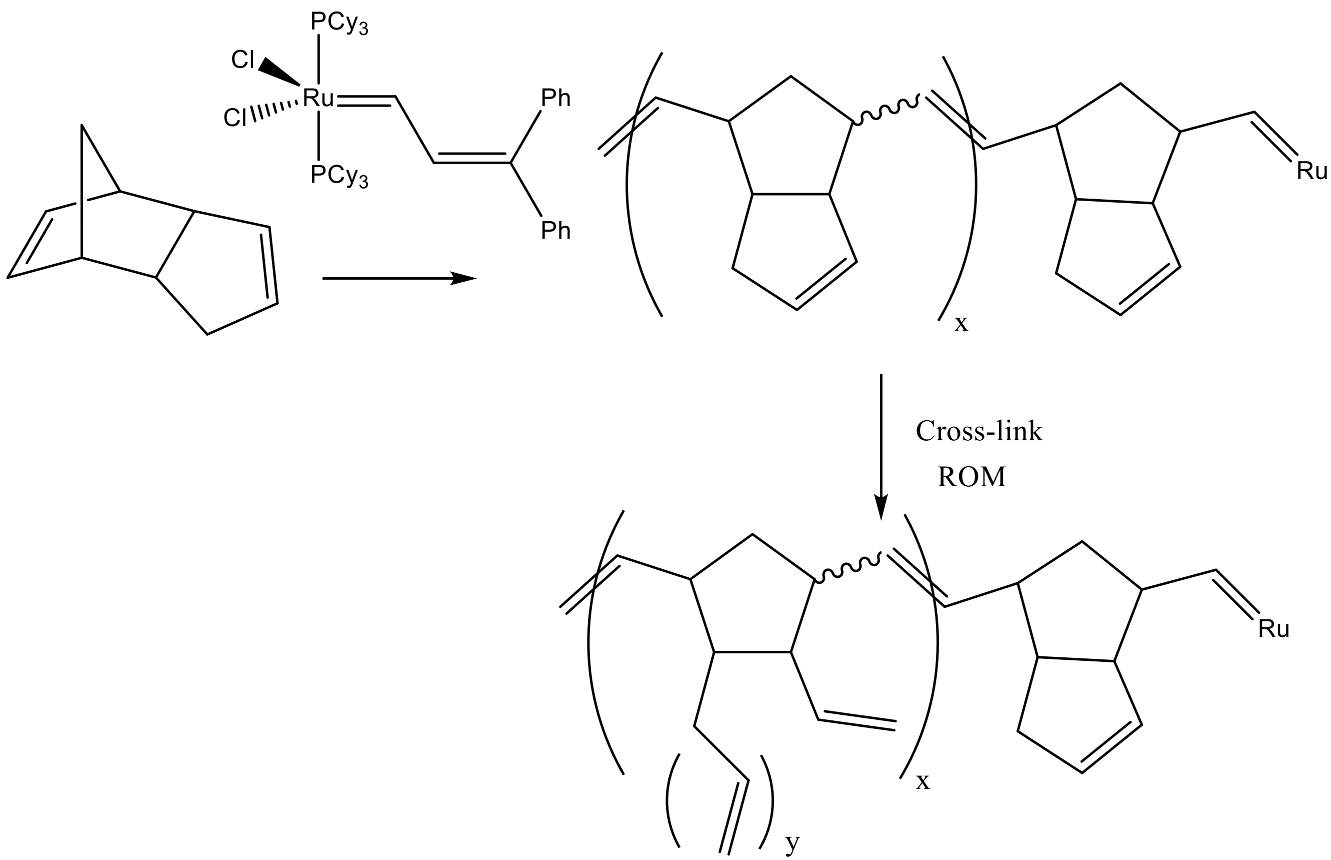
Bicyclic molecules with a lot of built-in ring strain such as norbornadiene and oxo-norbornadiene are transformed into useful polymers with ROMP.





Ring Opening Metathesis Polymerisation

Synthesis of crossed linked dicyclopentadiene.

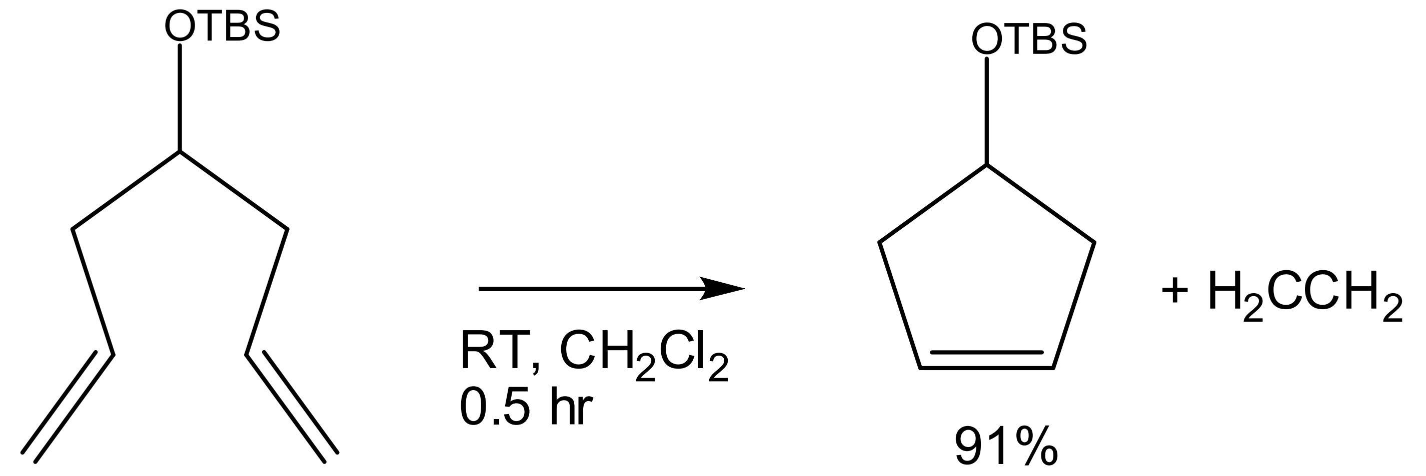


Ring Opening Metathesis Polymerisation

This additional cross-linking provides a "3rd dimension" polymeric networking. The result is a very strong thermo set material which can stop bullets!

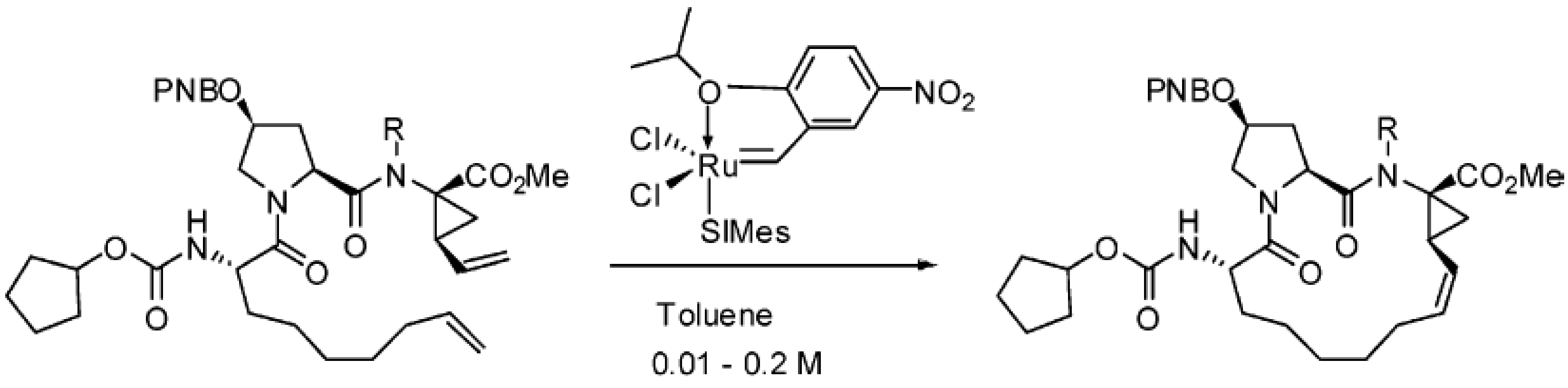
Ring Closing Metathesis (RCM)

The standard RCM reaction involves two double bonds joining to form one double bond.



RCM on an industrial scale

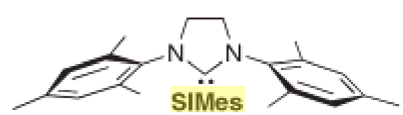
An Efficient Synthesis of HCV Protease Inhibitor BILN 2061:



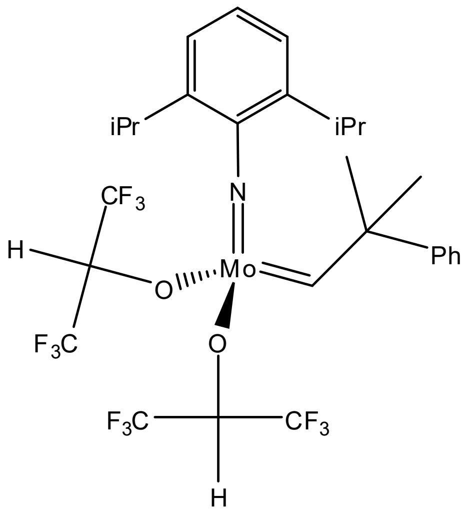
PNB = p-nitrobenzoyl

4a, R = H
4b, R = Boc

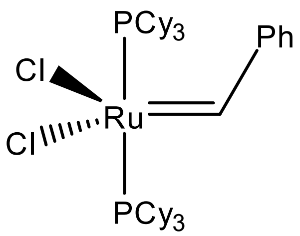
8a, 82% yield at 0.01 M
vs
8b, 93% yield at 0.2 M



Comparison of Schrock and Grubbs I catalysts in RCM



Schrock Catalyst



Grubbs I Catalyst

Metals : Mo and W

+ High activity

- Sensitive to air and H_2O
- Intolerant to polar functionalities

Metal : Ru

+ Functional group tolerant

- Lower activity and longevity

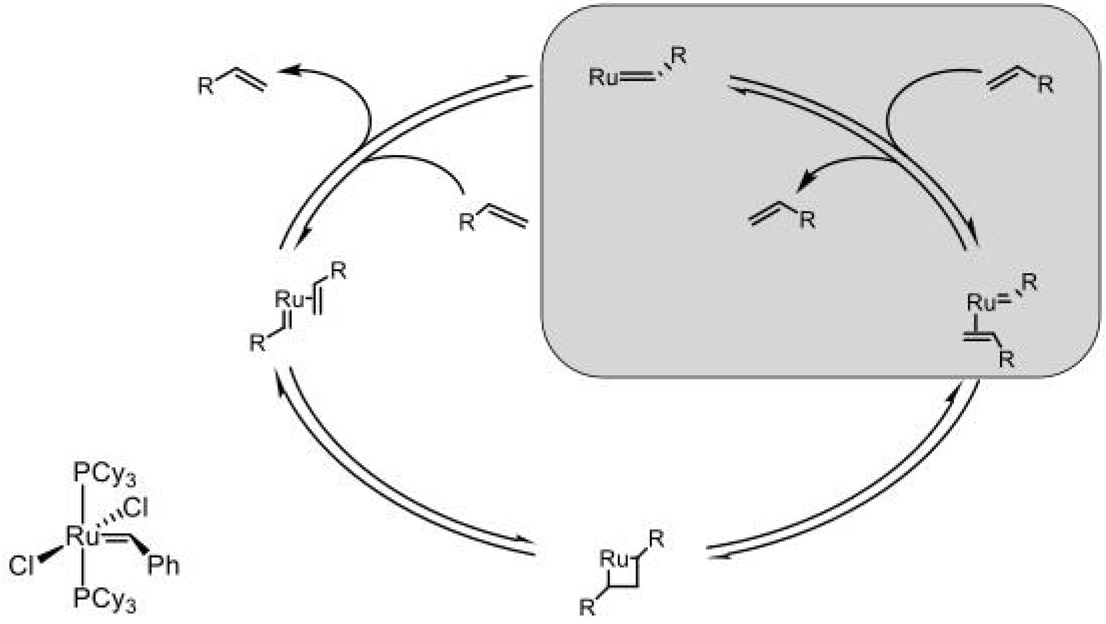
IV. Mechanism of a Typical Reaction

Relative Reactivity of Metals

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

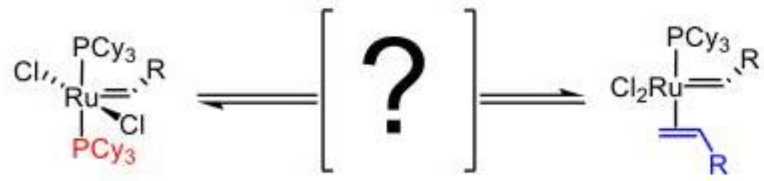
↑ Increasing Reactivity

The Catalytic Cycle



Grubbs 1st Generation

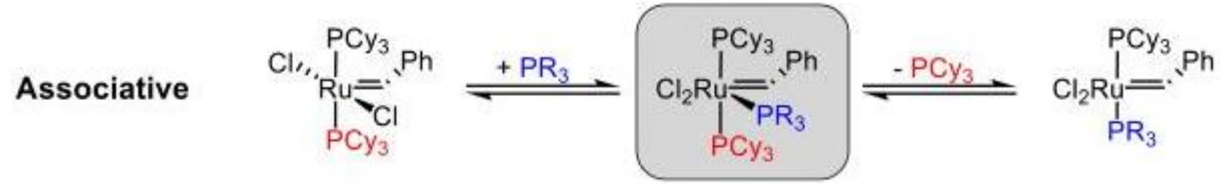
Mechanism of Olefin Coordination



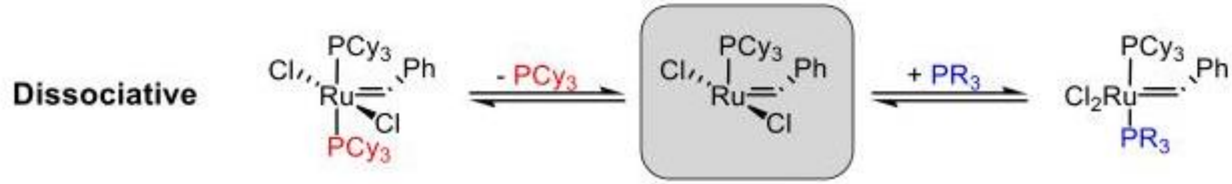
Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.

Phosphine Dissociation Experiments

How do we differentiate between the two pathways?



What do we expect



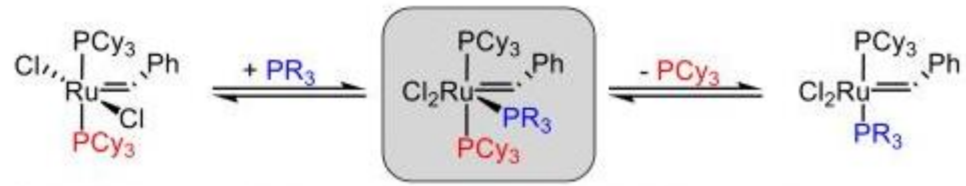
What do we expect

Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749.

Phosphine Dissociation Experiments

How do we differentiate between the two pathways?

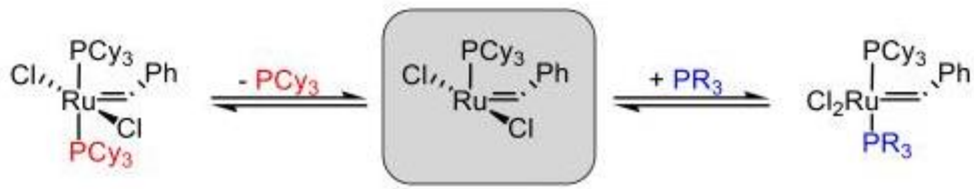
Associative



More ordered system, decrease in entropy: $\Delta S^{\ddagger}$ should be negative in sign

"S_N2 like": rate of dissociation is dependent on $[PR_3]$

Dissociative

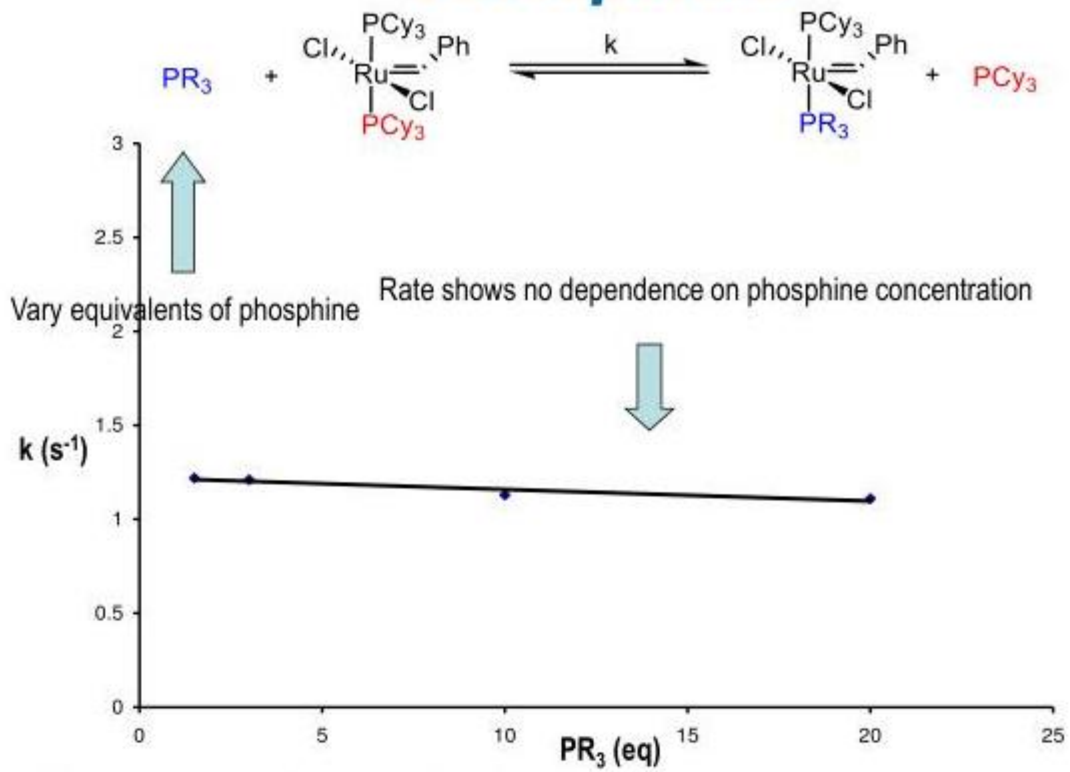


Less ordered system, increase in entropy: $\Delta S^{\ddagger}$ should be positive in sign

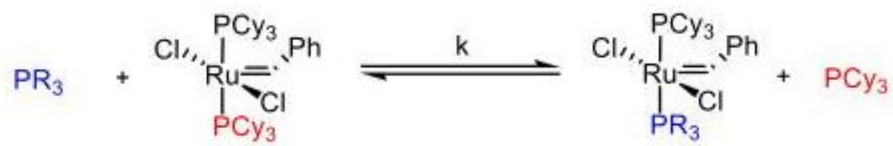
"S_N1 like": rate of dissociation is independent of $[PR_3]$

Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749.

Determining Dependence on Phosphine



Determining Entropy of Activation



Experimental data gives rate of reaction, k

How do we find ΔS from k?

Use the Eyring equation

The Eyring Equation

$$k = \frac{k_B T}{h} e^{-\frac{\Delta G}{RT}}$$

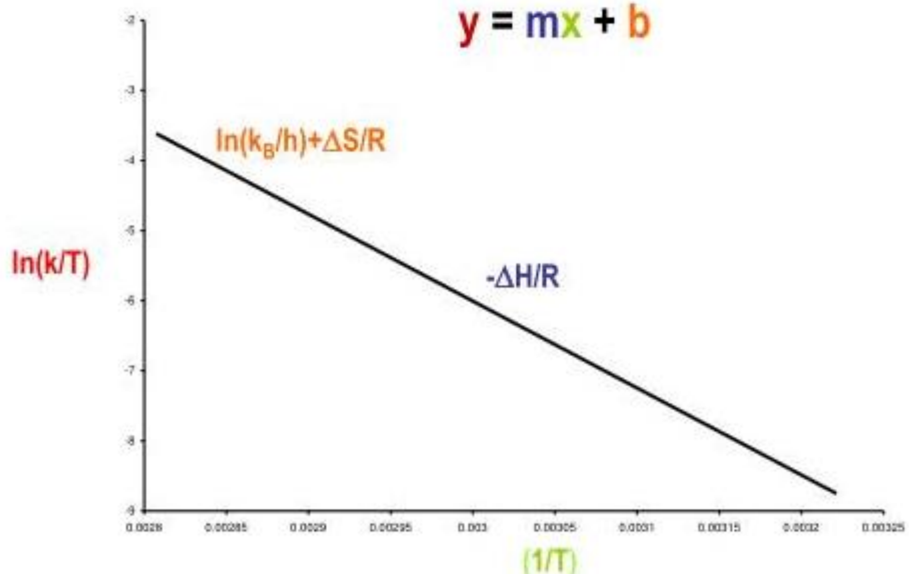
k = reaction rate constant
k_B = Boltzmann's constant
h = Planck's constant
T = temperature
ΔG = Gibbs energy of activation
R = Gas constant

Atwood, J. D. *Inorganic and Organometallic Reaction Mechanisms*; VCH: New York, 1997, p 13.

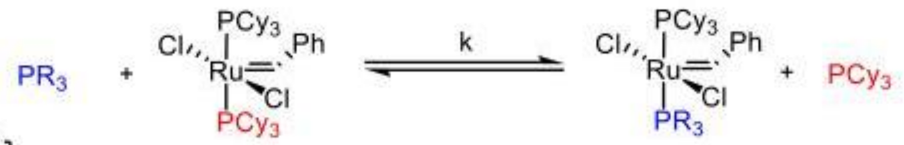
The Eyring Equation

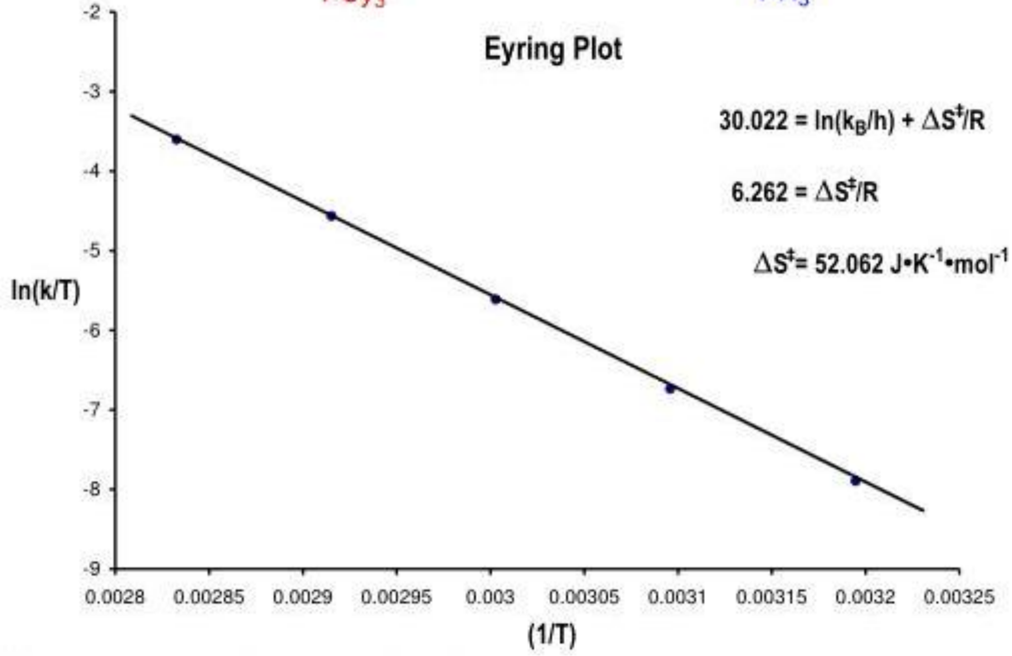
$$\ln\frac{k}{T} = \frac{-\Delta H}{R} \bullet \frac{1}{T} + \ln\frac{k_B}{h} + \frac{\Delta S}{R}$$

$$y = mx + b$$



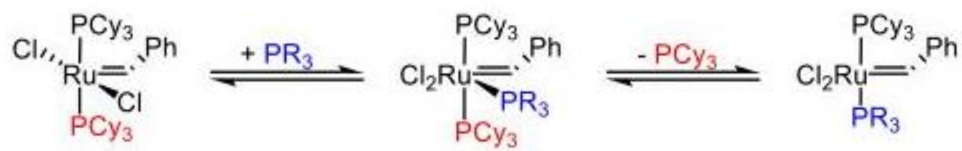
Determining Entropy of Activation





Determining Entropy of Activation

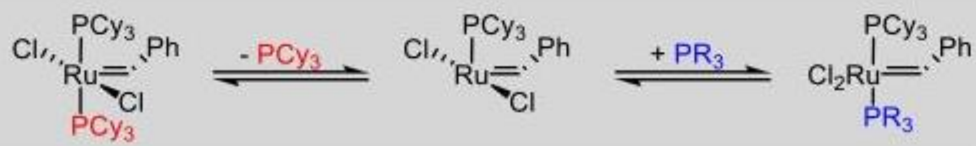
Associative



More ordered system, decrease in entropy: $\Delta S^{\ddagger}$ should be negative in sign

"S_N2 like": rate of dissociation is dependent on $[PR_3]$

Dissociative

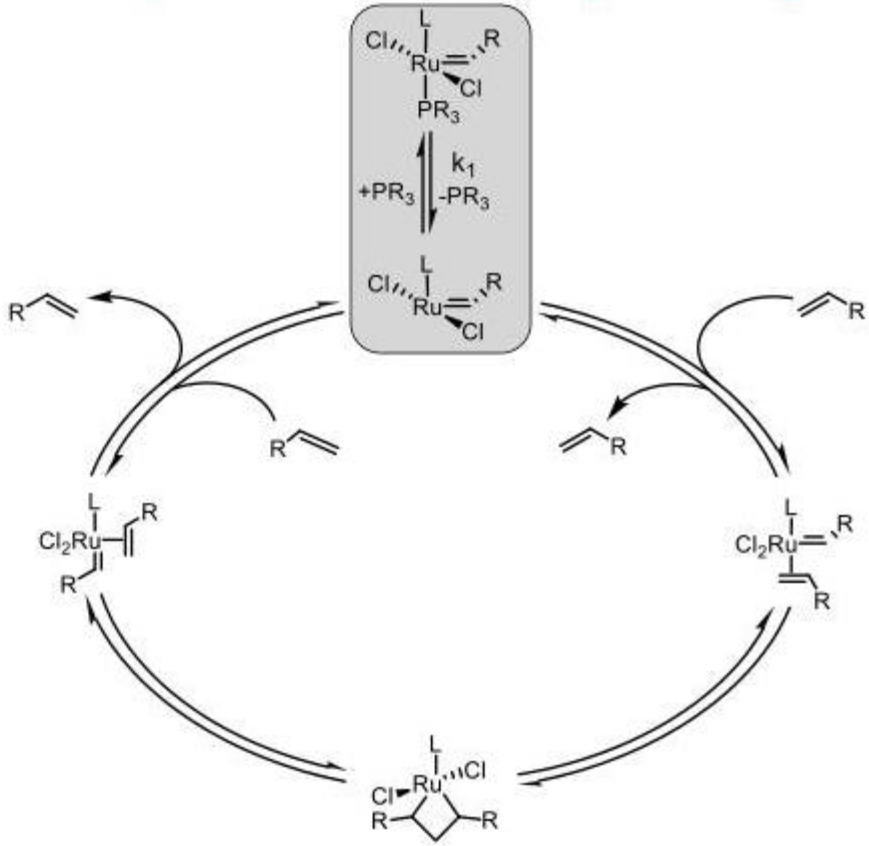


Less ordered system, increase in entropy: $\Delta S^{\ddagger}$ should be positive in sign

"S_N1 like": rate of dissociation is independent of $[PR_3]$

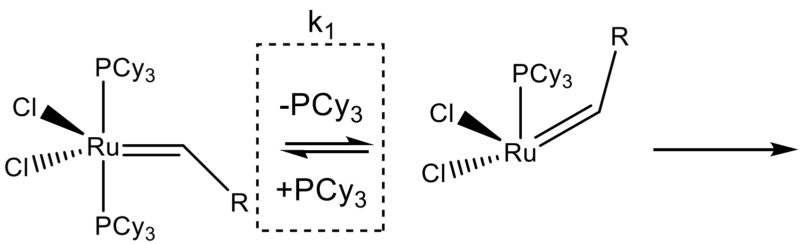
What other simple experiments you can propose to probe if it is dissociative?

The Updated Catalytic Cycle



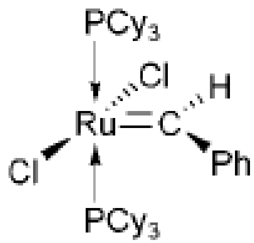
Rational catalyst improvements

Dissociative mechanism

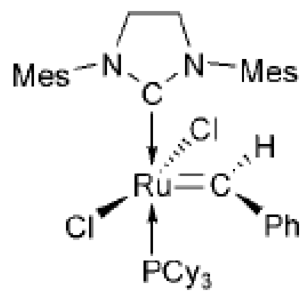


14 electron complex

Rational catalyst improvements

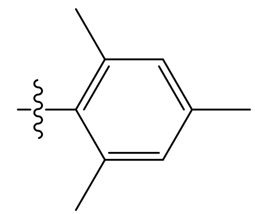


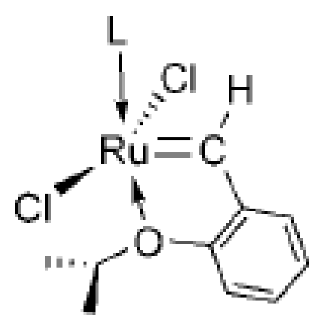
Grubbs catalyst
1st generation



Grubbs catalyst
2nd generation

The *N*-heterocyclic carbene effect (see below)
Mes =



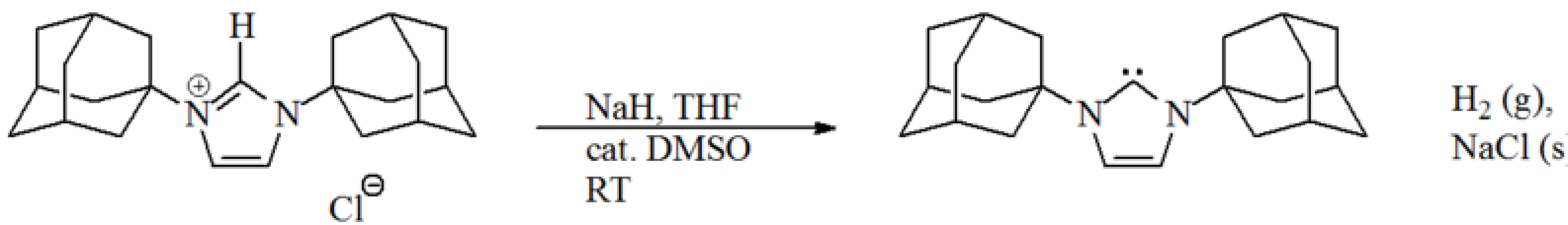


Grubbs-Hoveyda catalyst

The chelating carbene allows a very weak ligand to be used which allows the active 14 VE catalyst to be easily generated.

N-Heterocycle carbenes

Grubbs used carbenes derived from imidazolium rings (originally developed by Arduengo).



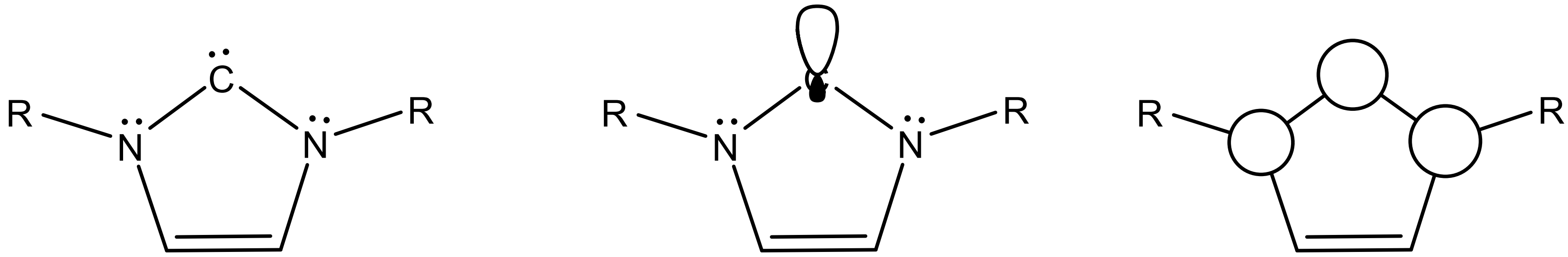
NHC is a persistent carbene, which is a carbene demonstrating particular stability despite also being a reactive intermediate.

The *instability* in these carbenes involves reactivity with substrates, or dimerisation.

Dimerisation is prevented by using bulky substituent groups.

N-Heterocycle carbenes

The C-H proton at the 2-position of the ring is very acidic and easily extracted to yield the carbene, in a singlet form:



The lone pair residues in the hybrid px+s orbital. The formal empty pz orbtial forms a π system, which forces the singlet configuration.

The lone pair is very basic because of this repulsion, hence they are highly reactive molecules.

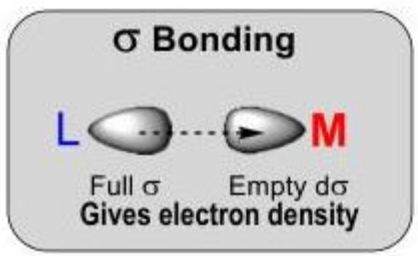
N-Heterocyclic Carbene Ligands

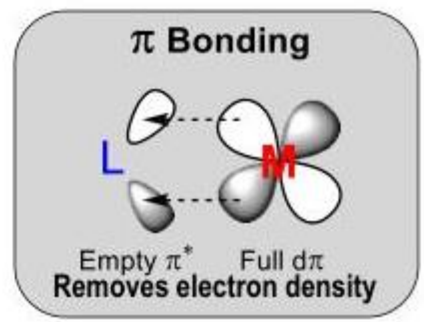
NHC ligand

Very basic
Excellent σ-donor
Poor π-acceptor

Phosphine ligand

Less basic
Good σ-donor
Poor π-acceptor

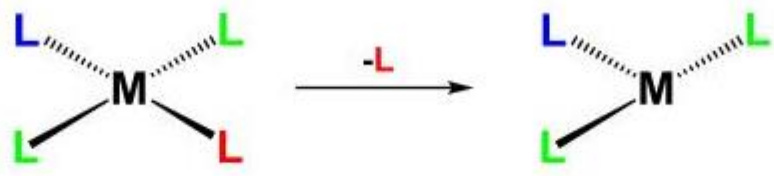




NHC ligation should result in metal with more electron-density

Diez-Gonzalez, S.; Nolan, S. P. *Coord. Chem. Rev.* **2006**, *251*, 874.
Straub, B. F. *Adv. Synth. Catal.* **2007**, *349*, 204.

The Trans Effect and Ligand Dissociation

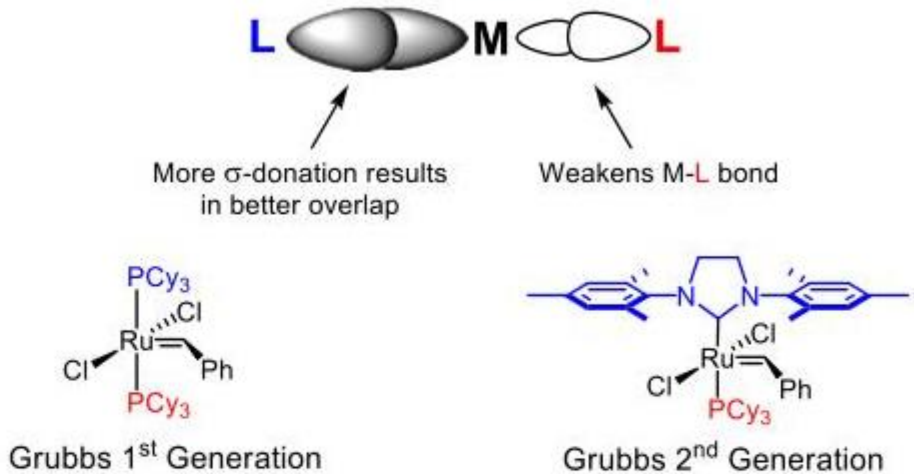


Change in electronics of L results in change rate of dissociation of L
Change in sterics of L has effect on dissociation of L

Electronics of ligand ***trans*** to L affects rate of dissociation

Atwood, J. D. *Inorganic and Organometallic Reaction Mechanisms*; VCH: New York, 1997, p 51.

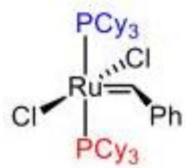
The Trans Effect and Ligand Dissociation



PCy_3 ligand should have a weaker bond in Grubbs 2

Which ligand favors phosphine dissociation?

The Trans *Effect and Ligand Dissociation*



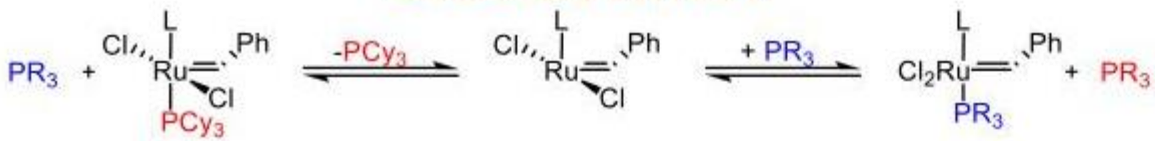
Grubbs 1st Generation

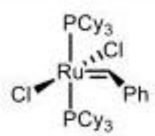
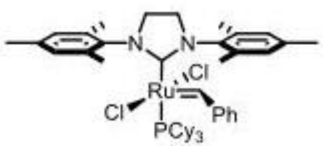
Grubbs 2nd Generation

PCy_3 ligand should have a weaker bond in Grubbs 2

Phosphine dissociation should be faster with Grubbs 2

Catalyst Activation by Phosphine Dissociation



Catalyst	Expected Result
	Slow
	Fast

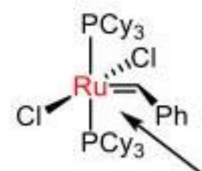
Difference of ~$\mathbf{10^2}$ in
rate of phosphine dissociation
in favor of Grubbs 1

Catalyst activity is NOT directly proportional to phosphine dissociation

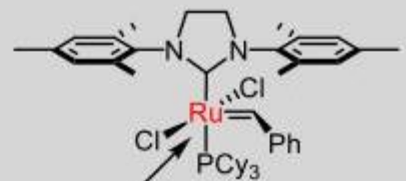
Why? What does it mean?

Ligand Effects on Catalytic Center

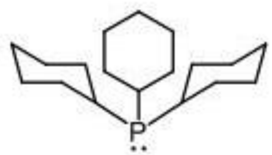
Grubbs 1st Generation



Grubbs 2nd Generation

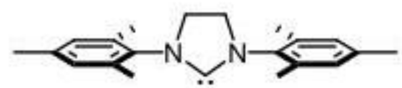


Should have more electron rich ruthenium



Phosphine ligand

Less basic
Good σ-donor
Poor π-acceptor



NHC ligand

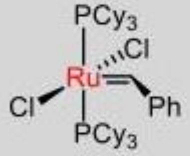
Very basic
Excellent σ-donor
Poor π-acceptor

Getty, K.; Delgado-Jaime, M. U.; Kennepohl, P. *J. Am. Chem. Soc.* **2007**, *129*, 15774.

Ligand Effects on Catalytic Center

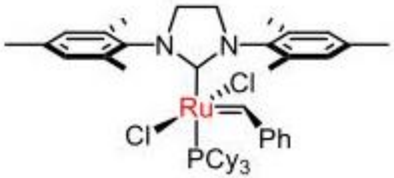
X-Ray Absorption Spectroscopy allows for determination of electronic state of ruthenium center

Grubbs 1st Generation



More electron rich

Grubbs 2nd Generation

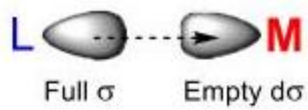


Why is Grubbs 2 electron-deficient?

Getty, K.; Delgado-Jaime, M. U.; Kennepohl, P. *J. Am. Chem. Soc.* **2007**, *129*, 15774.

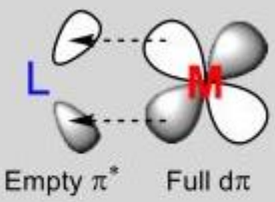
Ligand Effects on Catalytic Center

σ Bonding



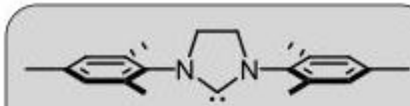
Gives electron density

π Bonding



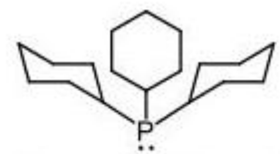
Removes electron density

DFT calculations show NHC can participate in π-bonding for this system



NHC ligand

Less overall donation due to π-bonding



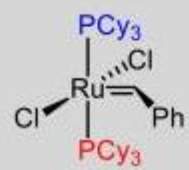
Phosphine ligand

Getty, K.; Delgado-Jaime, M. U.; Kennepohl, P. *J. Am. Chem. Soc.* **2007**, *129*, 15774.

The Trans Effect and Ligand Dissociation

More donation results in better overlap

Weakens M-X bond

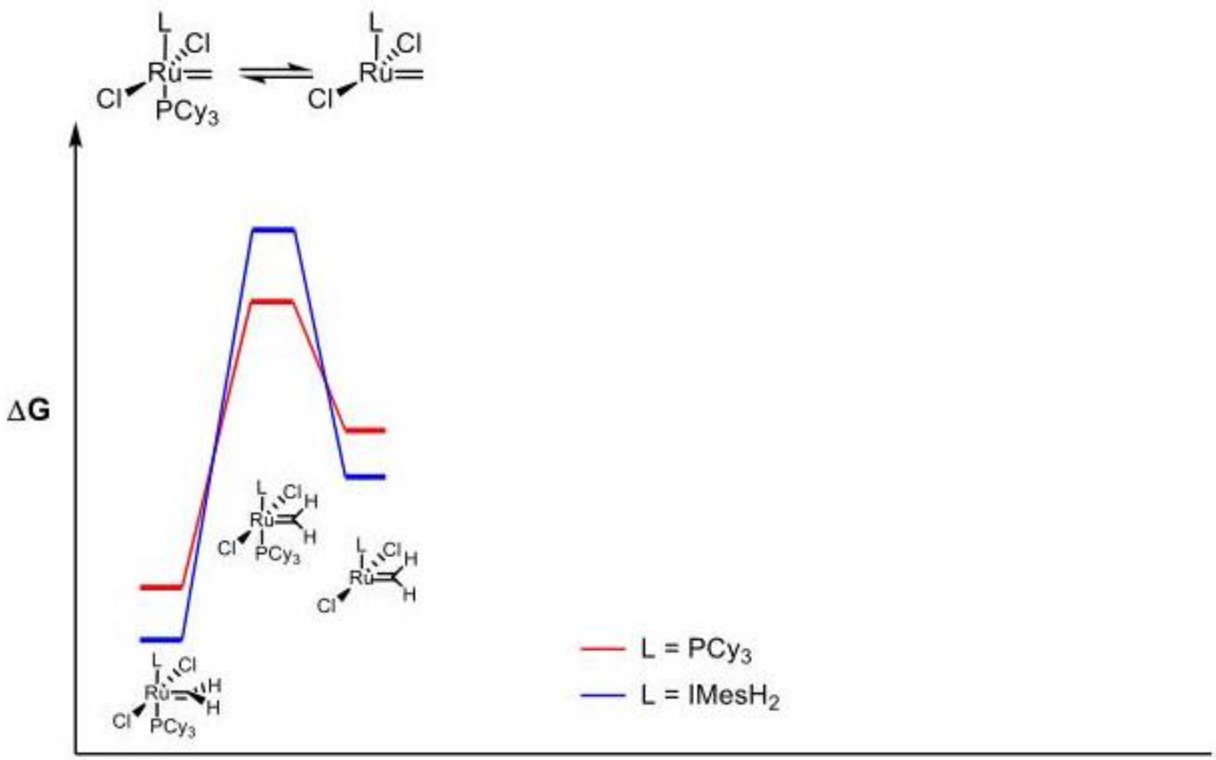


Grubbs 1st Generation

Should expect faster dissociation

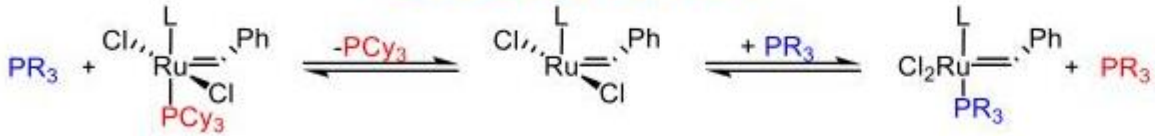
Grubbs 2nd Generation

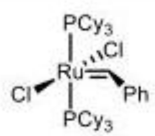
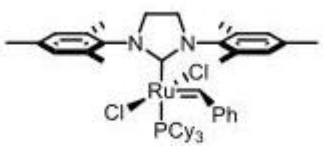
Reaction Pathway of Grubbs 1 and 2



Straub, B. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 5974.

Catalyst Activation by Phosphine Dissociation



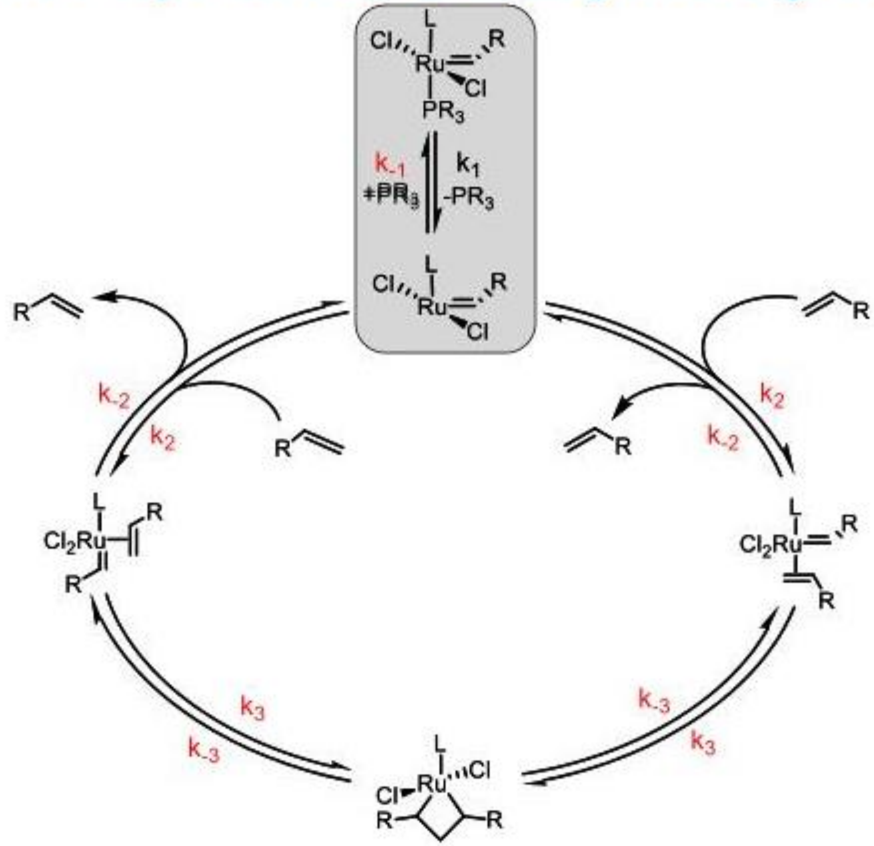
Catalyst	Expected Result
	Slow
	Fast

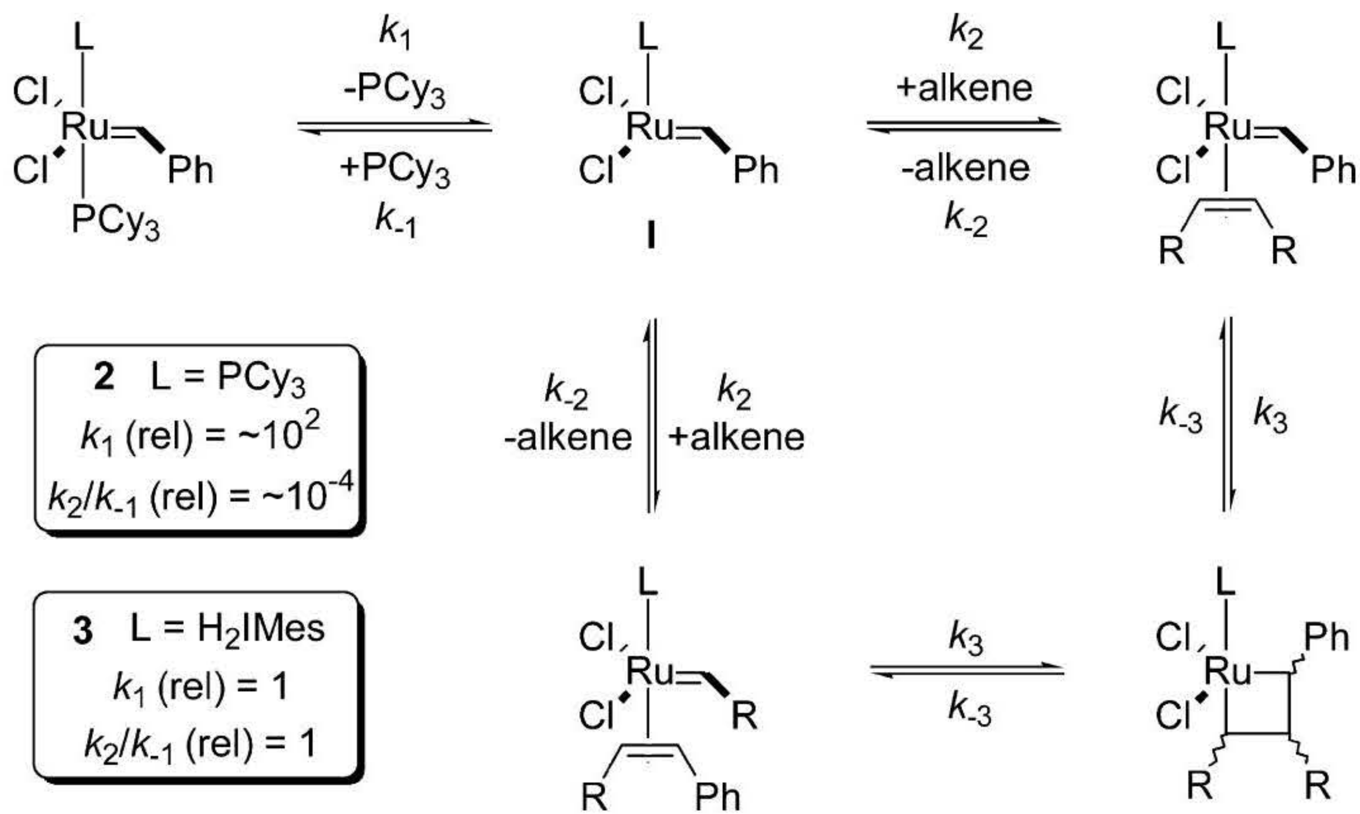
Difference of ~**10**^{2} in rate of phosphine dissociation in favor of Grubbs 1

Catalyst activity is NOT directly proportional to phosphine dissociation

Grubbs 2 must be more reactive once in the catalytic cycle

The Updated Catalytic Cycle





Higher activity of Grubbs II over Grubbs I is due to a larger k_2/k_{-1}.

Sanford, M.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

V. Rational improvements of catalysts based on mechanistic understanding

Depending on the application, it is dvantageous to employ catalysts that initiate more or less rapidly. For example, when performing ring-opening olefin metathesis polymerizations (ROMP) of strained cyclic olefinic monomers, slower-initiating catalysts are often desirable because they allow for longer handling of the monomer/catalyst resin before the polymerization starts.

Conversely, fast-initiating catalysts, able to promote metathesis at reduced temperatures, are useful in applications where low reaction temperatures are required to prevent catalyst decomposition and formation of undesired byproducts.

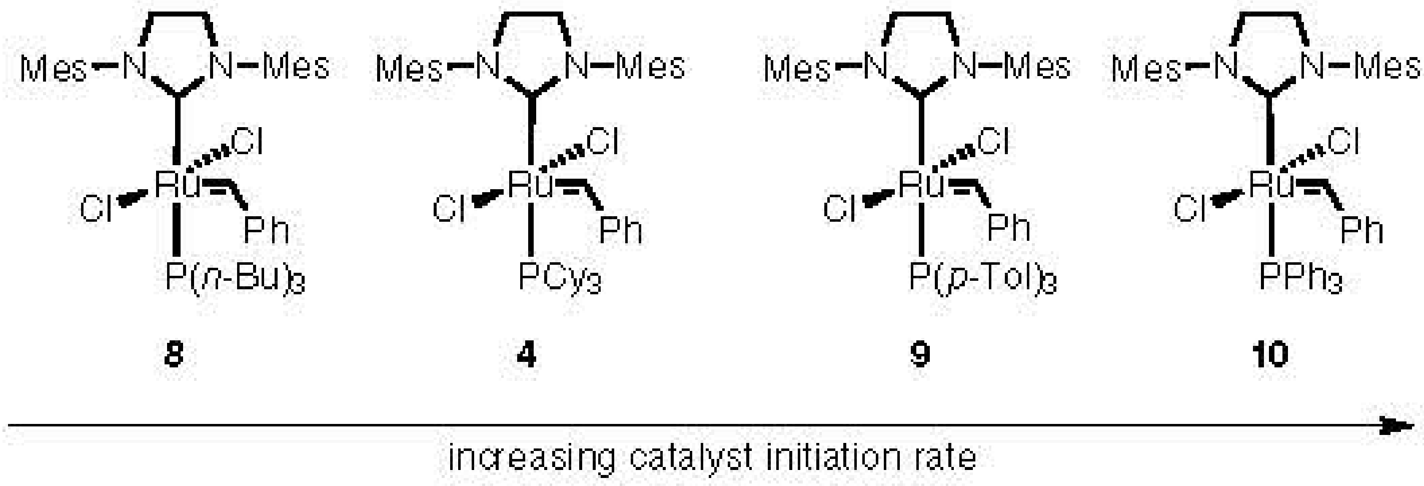


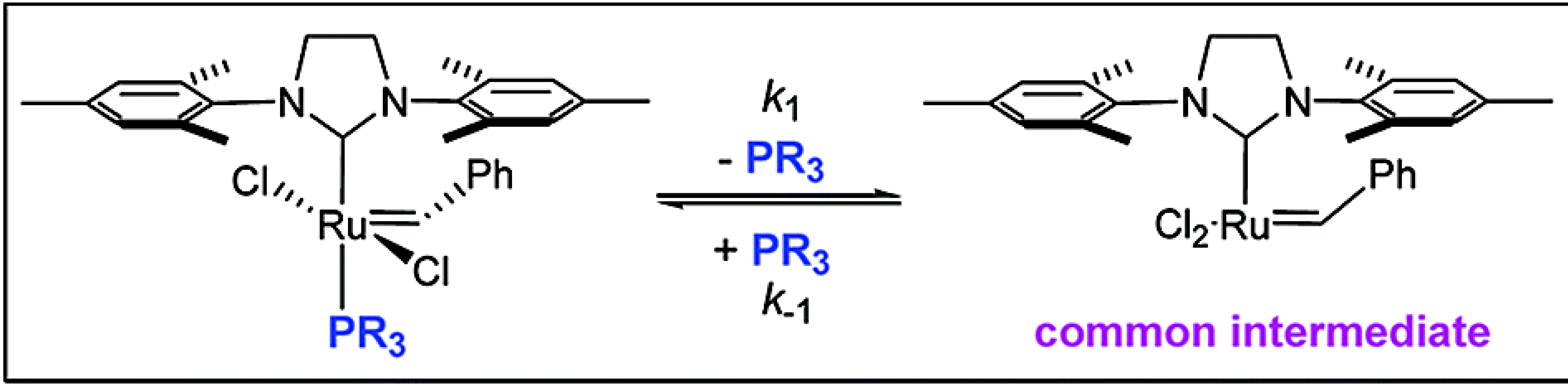
Figure 3. Effect of the Nature of the Phosphine Ligand on the Initiation Rate of the Second-Generation Catalyst.

Two reasons to explain; one more obvious and the other one more delicate

What is the obvious explanation for some of the trend?

1. A less electron donating phosphine is generally expected to be more labile;

Aryl phosphine is less electron donating (basic) than alkyl phosphine

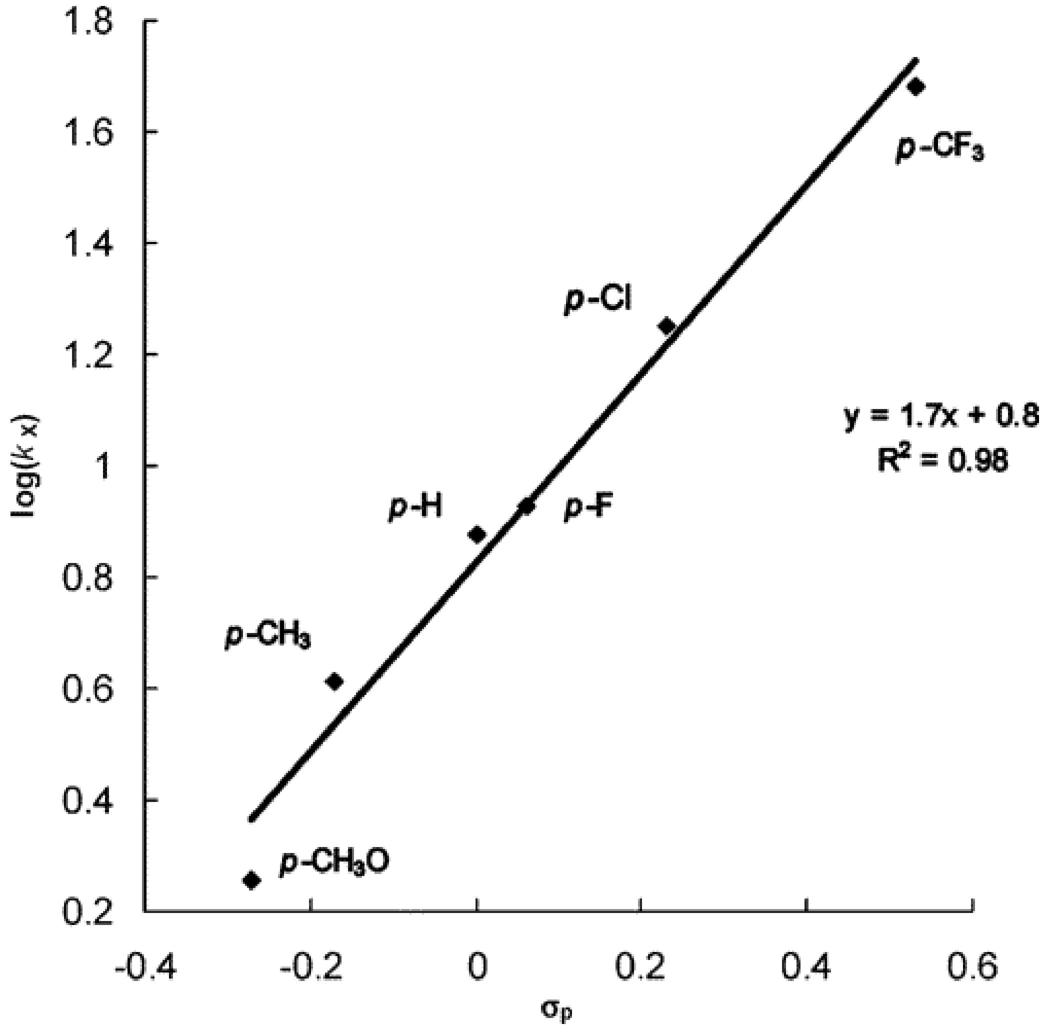


Increasing rate of initiation

$P(n\text{-Bu})_3$
PCy_3
$P(p\text{-}CH_3OC_6H_4)_3$
$P(p\text{-}CH_3C_6H_4)_3$
$P(C_6H_5)_3$
$P(p\text{-}FC_6H_4)_3$
$P(p\text{-}ClC_6H_4)_3$
$P(p\text{-}CF_3C_6H_4)_3$

J. Am. Chem. Soc. 2003, 125, 33, 10103-10109

Linear free energy correlation



σ_p = Hammett constant, related to electronic property.
The smaller the more electron rich

2. In some cases phosphine pK_a and k_1 (dissociation) not linear; For example,PBn_3 and PCy_3 initiate at similar rate, but conjugated acids have pKa of 6 and 9.7, respectively.

Complexities of the steric and electronic changes from phosphine variation.

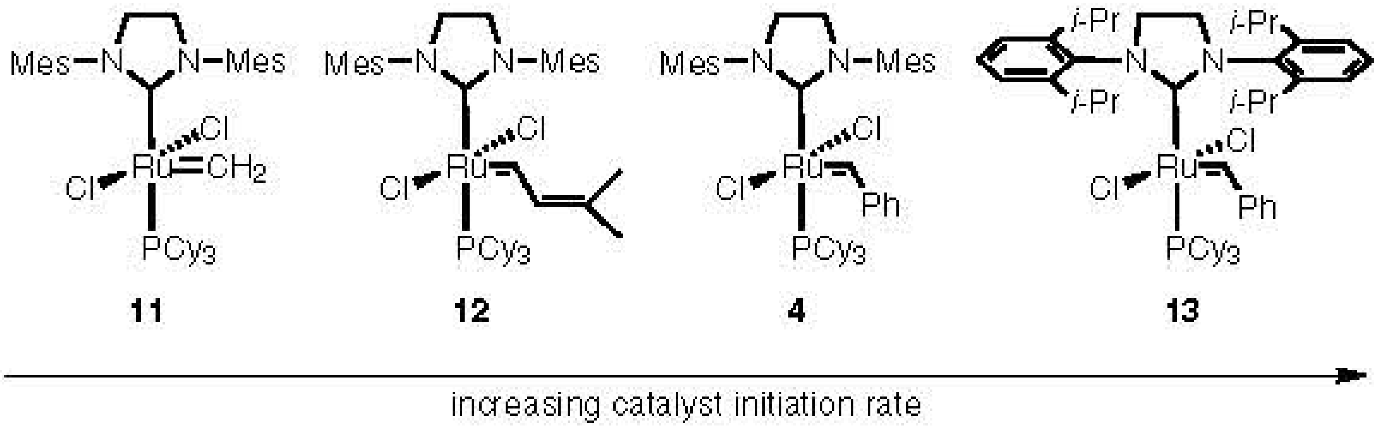


Figure 4. Influence of the Nature of the Alkylidene and NHC Ligands on the Initiation Rate of the Second-Generation Catalyst.

Sterically bulky and electron-donating groups (e.g., alkyl) on alkylidene lead to higher initiation rates because …

New approach: use a stable 14 VE catalyst

$$[Cl_2(L)(L')Ru{=}C(H)R] \rightleftharpoons [Cl_2(L)Ru{=}C(H)R] + L'$$

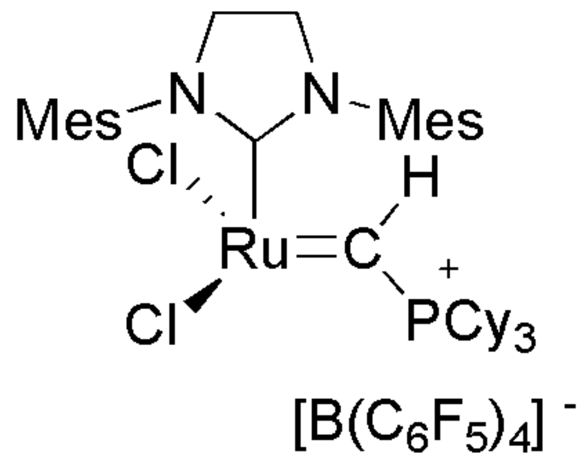
New Catalyst Precursor

Direct access to the active species

No free L' >>> no interference

The catalyst

4-coordinate, 14 e$^-$ phosphonium alkylidene

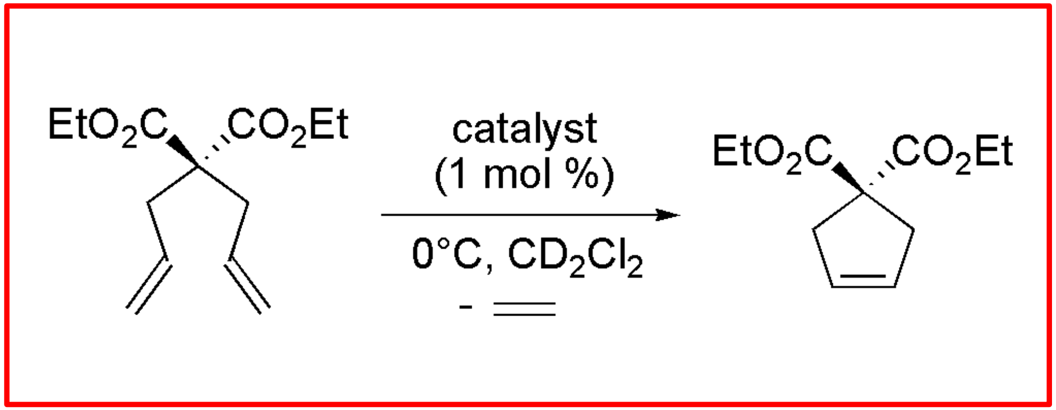


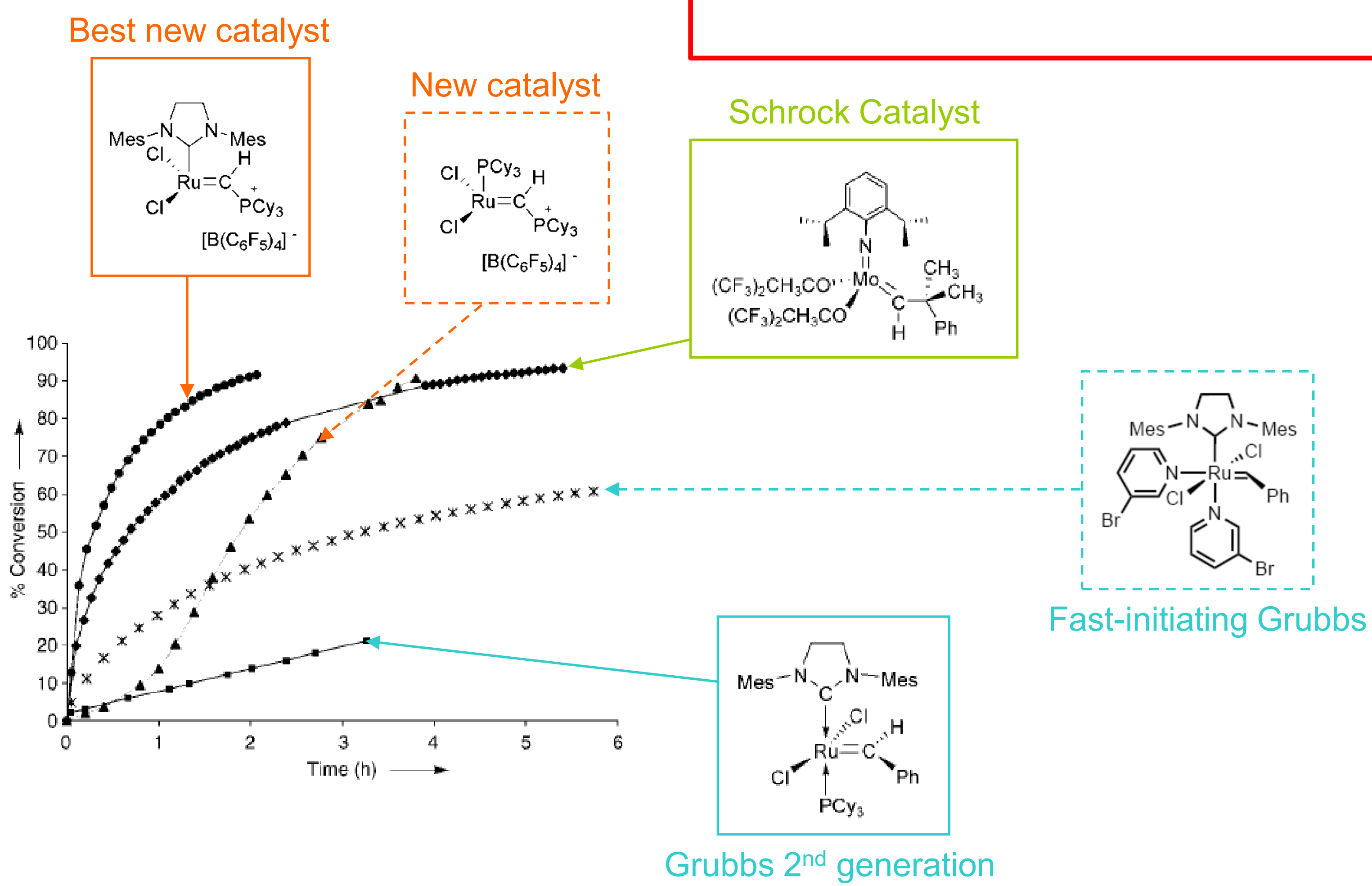
The bulky substituent on the carbene stabilizes the vacant coordination site.

Distorted trigonal pyramid
Stable to oxygen and moisture in solution
No evidence for a C-H agostic interaction

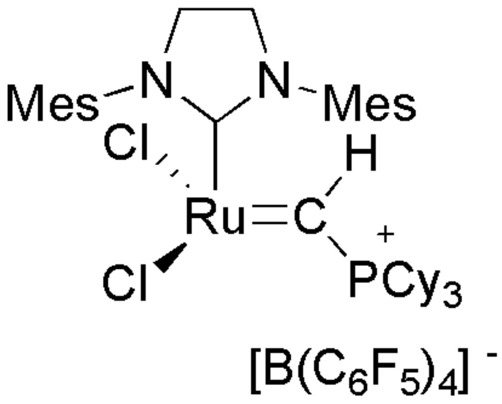
Piers et al.

RCM test reaction





Why is the catalyst so active ?



No phosphine dissociation step

No free phosphine

All Ru present is active

Initiation : olefin-binding event

Summary

- History
- Electronic structures of catalysts
- Synthetic applications – ROMP and RCM
- Mechanism of a Typical Reaction
- Rational improvement of catalysts based on mechanistic understanding