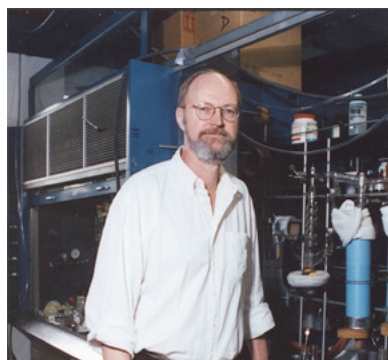


*A Small Portion of the Career of  
Robert Grubbs*

*RuCl<sub>3</sub> to N-Heterocyclic Carbenes*

Sean Brown  
MacMillan group meeting  
5/5/04



*Biographical Notes*

1963 B.S. University of Florida  
1965 M.S. University of Florida (M. A. Battiste)  
1968 Ph.D. Columbia University (Ronald Breslow)  
1969 Postdoc Stanford University (J. P. Collman)

Professor, Michigan State University 1969-1978  
Caltech 1978-present  
Victor and Elizabeth Atkins Professor  
of Chemistry 1990- present

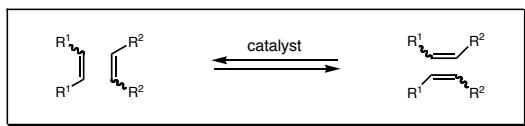
■ some notable coworkers

Prof. Scott Miller, Boston College  
Prof. Gregory Fu, MIT  
Prof. Geoffrey Coates, Cornell University  
Prof. SonBinh Nguyen, Northwestern University  
Prof. Stephen Buchwald, MIT  
Prof. Dean Toste, UC-Berkeley

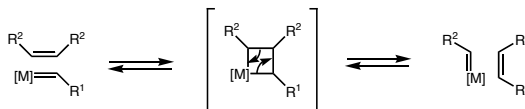
Organization of Presentation

- Olefin metathesis introduction
  - Ruthenium revisited
  - Bisphosphine systems
  - N-Heterocyclic carbenes

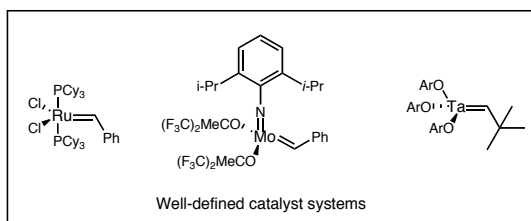
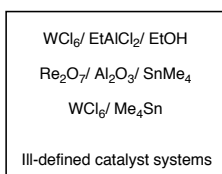
## Olefin Metathesis: Introduction



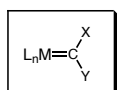
- Chauvin-type mechanism: model proceeds through a metallacyclobutane intermediate



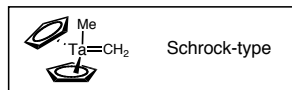
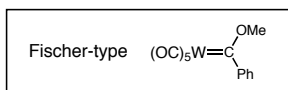
- Catalyst systems



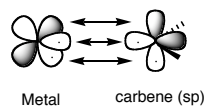
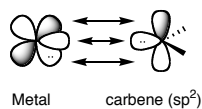
## Background: Metal Carbenes



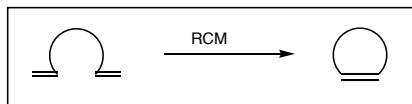
- Definition: Transition metal complex possessing a formal metal to carbon double bond
- X, Y = alkyl, aryl, H, or heteroatom (O, N, S, Halogen)
- Two types of metal carbenes: Fischer-type and Schrock-type



- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>■ low oxidation state middle to late TM</li> <li>■ Substituents (X &amp; Y): at least one electronegative atom</li> <li>■ Ligands are generally good <math>\pi</math> acceptors</li> <li>■ Electrophilic carbenes: nucleophile attacks at <math>\text{C}_{\text{carbene}}</math></li> <li>■ <math>\text{C}_{\text{carbene}}</math> is L-type ligand: Metal oxidation state unchanged</li> </ul> | <ul style="list-style-type: none"> <li>■ high oxidation state early TM</li> <li>■ Substituents (X &amp; Y) are H or alkyl</li> <li>■ Ligands are generally good <math>\sigma</math> or <math>\pi</math> donors</li> <li>■ Nucleophilic carbenes: electrophile attacks at <math>\text{C}_{\text{carbene}}</math></li> <li>■ <math>\text{C}_{\text{carbene}}</math> is <math>\text{X}_2</math>-type ligand: metal oxidation state changed by +2</li> </ul> |
|--|--|

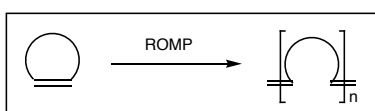


### Fundamental Olefin Metathesis Reactions



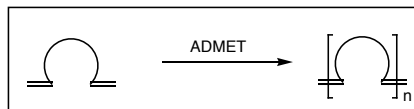
Ring Closing Metathesis (RCM)

Cross Metathesis (CM)



Ring Opening Metathesis Polymerization (ROMP)

Acyclic Diene Metathesis Polymerization (ADMET)



### Why Ruthenium?

	Titanium	Tungsten	Molybdenum	Ruthenium
Increasing Reactivity	Acids	Acids	Acids	<b>Olefins</b>
	Alcohols, Water	Alcohols, Water	Alcohols, Water	Acids
	Aldehydes	Aldehydes	Aldehydes	Alcohols, Water
	Ketones	Ketones	<b>Olefins</b>	Aldehydes
	Esters, Amides	<b>Olefins</b>	Ketones	Ketones
	<b>Olefins</b>	Esters, Amides	Esters, Amides	Esters, Amides

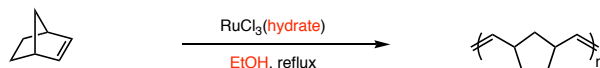
■ Ti, W, Mo are very active metathesis catalysts, but lack functional group tolerance

■ Ru is a much more selective catalyst but is very unreactive

Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

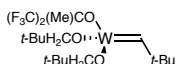
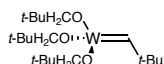
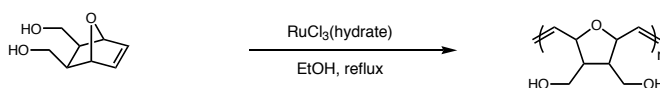
### Ruthenium Revisited

- ROMP of norbornene derivatives with  $\text{RuCl}_3$  in protic solvents was an important but overlooked first step toward a functional tolerant olefin metathesis catalyst



Michelotti, F. W., Keaveney, W. P. *J. Polym. Sci.* **1965**, A3,895.

- First report of ROMP of 7-oxabicyclo[2.2.1]hept-5-ene

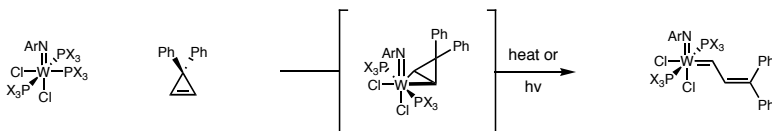


- No ROMP products were observed from the well-defined tungsten alkylidines

Novak, B. M., Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, 110, 960.

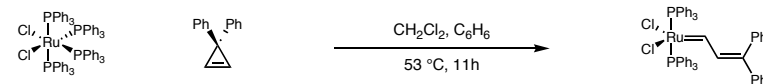
### The First Metathesis Active Ruthenium Alkylidene

- Synthesis of tungsten alkylidines from diphenylcyclopropene



Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, 115, 8130.

- Synthesis of the first well-defined metathesis active ruthenium alkylidene

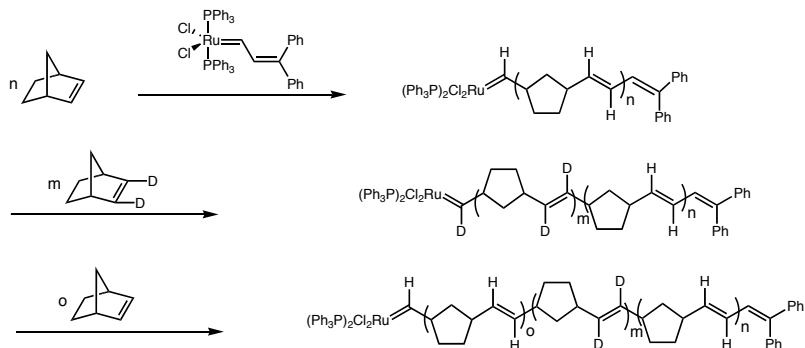


- The vinyl ruthenium carbene complex is stable to air, protic solvents, and acidic solutions

- ROMP is limited to strained monomers but the ruthenium alkylidene allows for increased functional group tolerance

Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, 114, 3974.

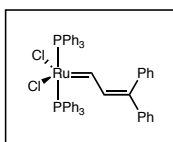
### ROMP of Norbornene: It's Alive



- The propagating alkydine is observed by  $^1\text{H}$  NMR, but disappears upon addition of deuterated monomer and reappears after addition of non-deuterated monomer
- This system is living because the propagating alkydine is stable on the time scale of the reaction
- Polymerization occurs quantitatively upon further additions of monomer several hours after the previous amount was consumed

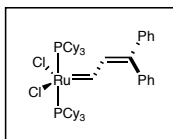
Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, 114, 3974.

### Basic Phosphines Increase Metathesis Activity



- Greater functional group tolerance, but ROMP is limited to highly strained monomers

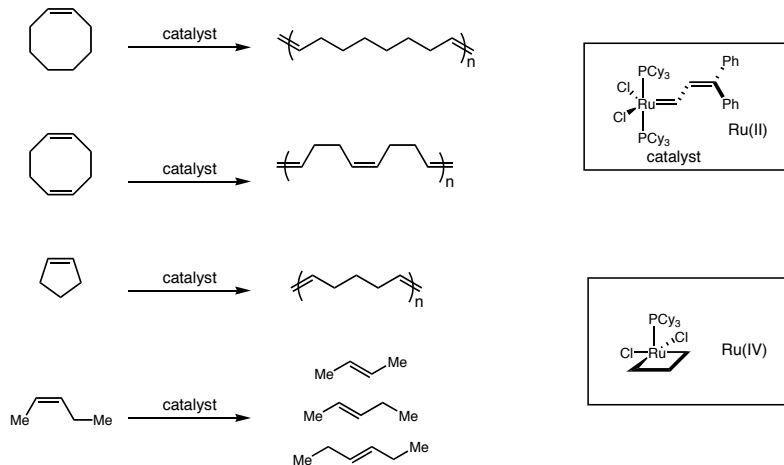
- Previously in early transition metal systems metathesis activity increased with less basic ligands
- Variety of electron-withdrawing and cationic ligands, as well as, less basic phosphines showed no improvement



- The larger more basic  $\text{PCy}_3$  ligand gives greater metathesis activity
- First ruthenium complex active toward acyclic olefins

Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, 115, 9858.

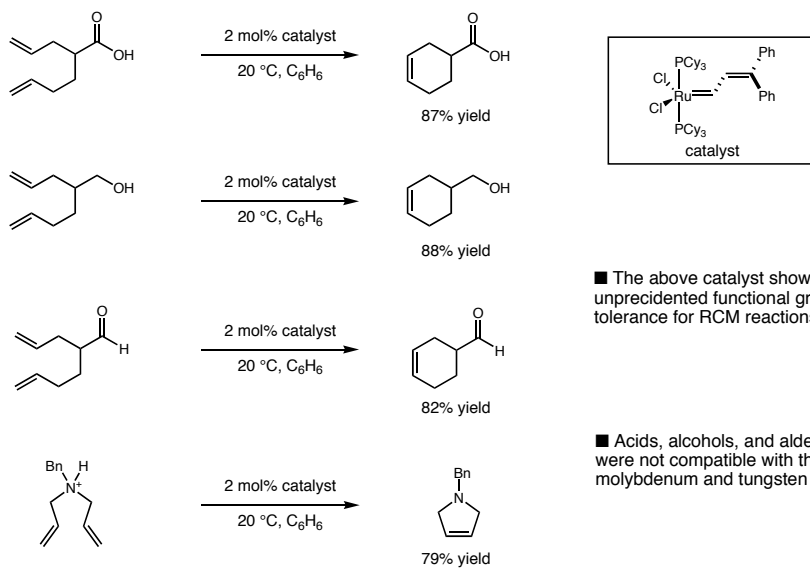
### ROMP of Low Strain Monomers



■ Good  $\sigma$ -donors stabilize the electron poor metallacyclobutane

Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, 115, 9858.

### RCM with Ruthenium Alkyldines

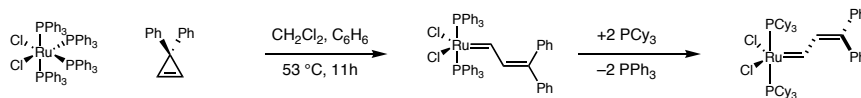


■ The above catalyst shows unprecedented functional group tolerance for RCM reactions

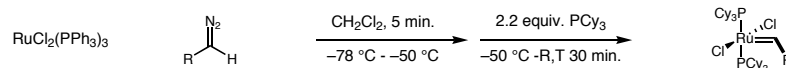
■ Acids, alcohols, and aldehydes were not compatible with the molybdenum and tungsten systems

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

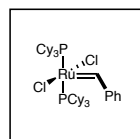
### RCM with Ruthenium Alkyldines



- Diphenylcyclopropene was difficult to synthesize and did not allow for differentiation at the alkyldine



- Synthesis of ruthenium alkyldines from diazocompounds allows for systematic evaluation of alkyldine



- Phenyl substituted carbene combines the best initiation properties and stability

- The combination of strong  $\sigma$ -donating PCy<sub>3</sub> ligands, readily initiated benzyldiene, and functional tolerant ruthenium metal center attributed to wide use of this catalyst

Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, 118, 100.

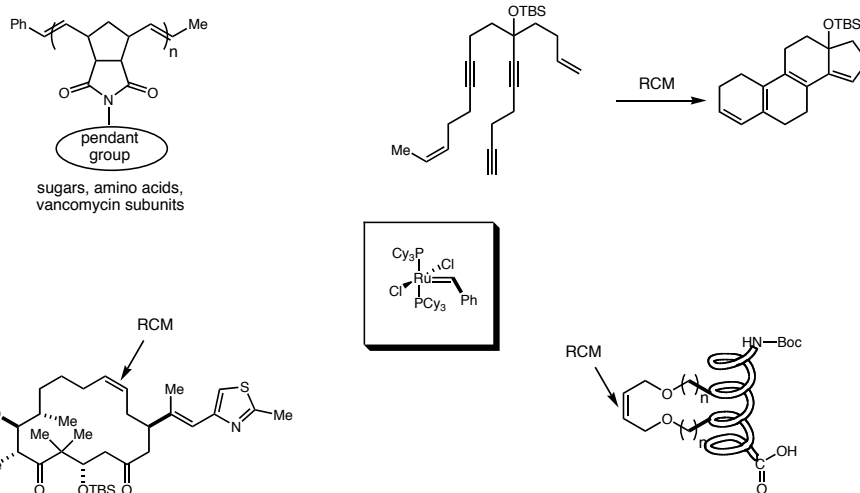
### Olefin Metathesis

- In 1990 there were only 35 publications regarding the topic of olefin metathesis
- In 1999 the number of publications increased to 250
- In 1999, 75% of these publications used a ruthenium-based catalyst system
- In 1999, 62% of the publications specifically used the Grubbs vinylidene or benzyldiene catalysts



Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, 34, 18.

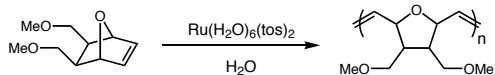
### Functional Group Tolerance



■ Functional group tolerance of the ruthenium benzylidene allowed wide application of metathesis methodology

Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, 34, 18.

### Living ROMP in water

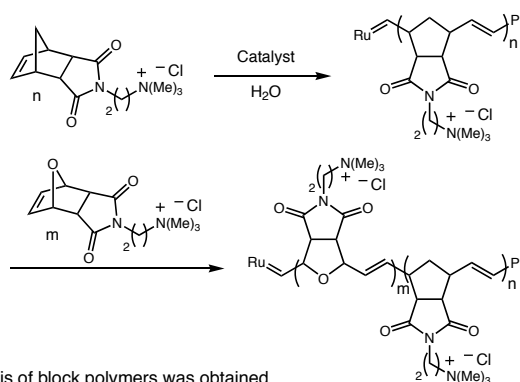
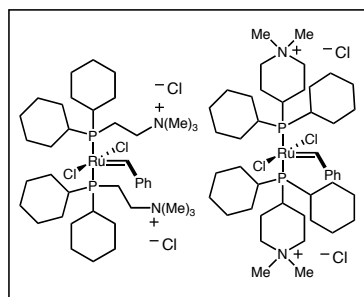


Novak, B. M., Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, 110, 7542.

■ Though ROMP of norbornene derivatives in water had been achieved the catalyst were ill-defined and the propagating species short lived

■ Living polymerization in water has been a goal of polymer chemistry, because it should allow construction of water soluble polymers in a precise fashion

■ Grubbs benzylidene catalyst is insoluble and inactive in water



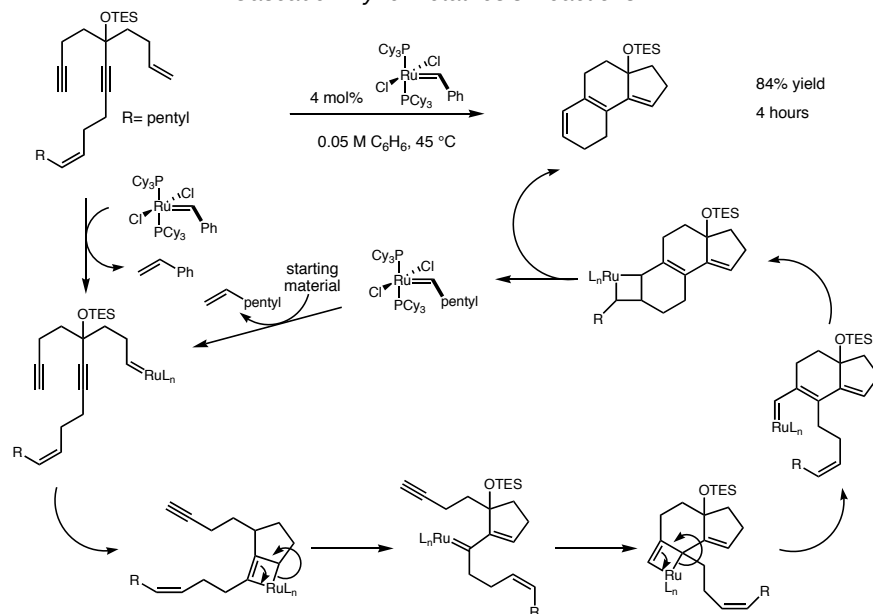
■ First example of a living polymerization in water

■ The propagating species are stable and synthesis of block polymers was obtained

Lynn, D. M.; Mohr, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, 120, 1627.



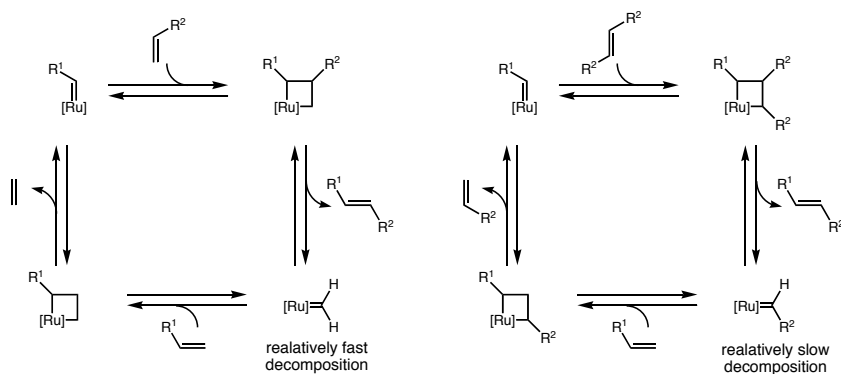
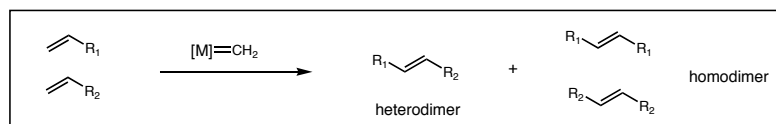
### Cascade Enyne Metathesis Reactions



■ Olefin metathesis provides efficient route to polycyclic molecules from acyclic precursors

Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, 63, 4291.

### Cross Metathesis

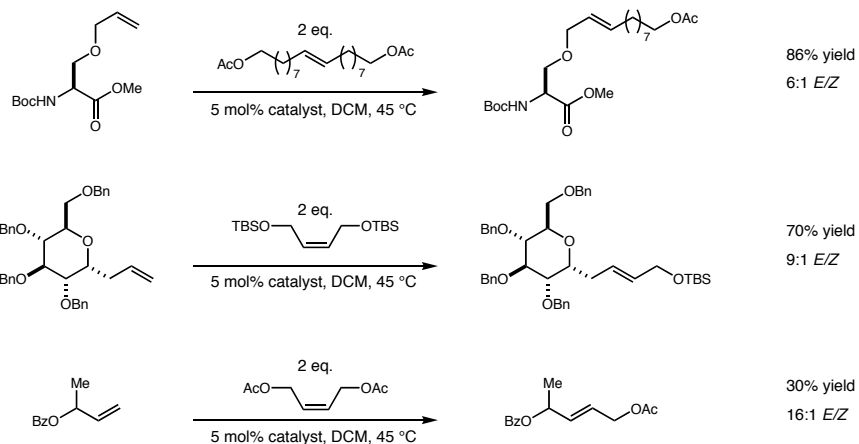
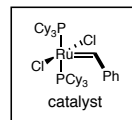


■ Metathesis occurs faster and in higher yields using one component as a homodimer

Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, 122, 58.

### Cross Metathesis

■ Cross metathesis of variety functionally diverse olefins occurs with the Grubbs ruthenium benzylidene catalyst

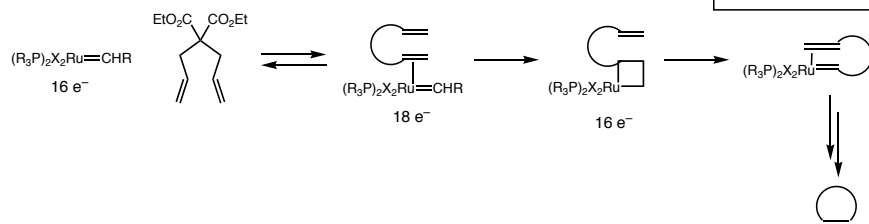


■ Limitations include sterically bulky olefins and olefins conjugated to electron withdrawing groups

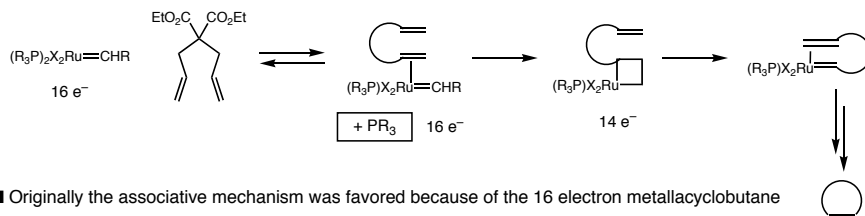
Blackwell, H. E.; O'Leary, D. J.; Chatterjee A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, 122, 58.

### Associative vs. Dissociative Mechanism

■ Associative mechanism



■ Dissociative mechanism



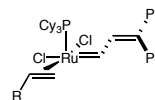
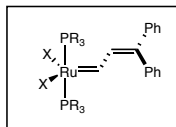
■ Originally the associative mechanism was favored because of the 16 electron metallacyclobutane

■ Kinetic studies favor the dissociative mechanism: excess phosphine severely retards metathesis rate

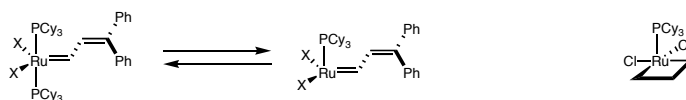
Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, 119, 3887.

### Ligand Effects

PR <sub>3</sub>	X	turnovers/ h
PCy <sub>3</sub>	Cl	19.0
	Br	15.4
	I	1.4
PCy <sub>2</sub> Ph	Cl	8.0
	Br	4.5
	I	na
P <i>t</i> -Pr <sub>3</sub>	Cl	17.5
	Br	13.9
	I	1.1
P <i>t</i> -Pr <sub>2</sub> Ph	Cl	5.5
	Br	2.3
	I	na



■ The weakly σ-donating chlorine allows for a strong association between the *trans* olefin and the ruthenium metal center

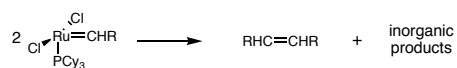
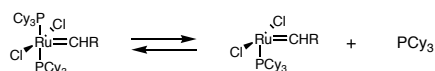


■ Strong σ-donating phosphines may promote formation of the monophosphine complex and also stabilizes the 14-electron metallacyclobutane

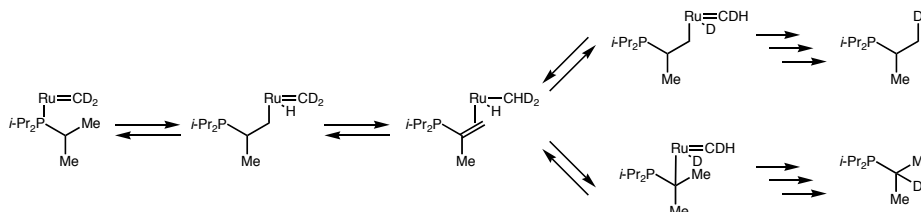
Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, 119, 3887.

### Decomposition of Ruthenium Carbenes

Carbene	Temp.	Conc.	Half-Life
	55 °C	0.023 M	8 h
	55 °C	0.023 M	40 min.
	55 °C	0.023 M	8 days



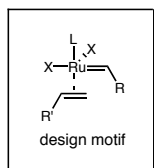
■ Ruthenium alkylidene decomposition occurs through a bimolecular process preceded by phosphine dissociation



■ Decomposition of the ruthenium methylidene is a unimolecular process with little dependence on phosphine

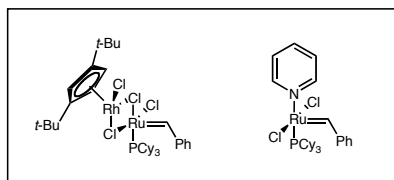
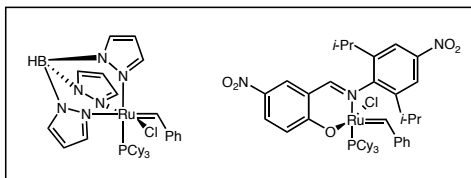
Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, 64, 7202.

### New Catalyst Design Motif



■ Mechanistic studies showed that the formation of a highly active monophosphine intermediate is necessary for catalyst activity

■ Catalysts suffer from low reactivity because the phosphines are not labile enough for catalyst activation



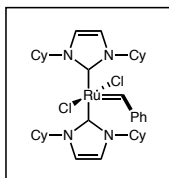
■ Highly active catalysts but increased decomposition

■ Ancillary ligands do not stabilize metathesis intermediates

■ Ancillary ligands that too labile form high concentrations of monophosphine intermediate which accelerates metathesis, as well as, decomposition

Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, 34, 18.

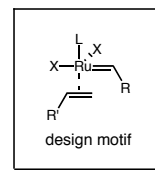
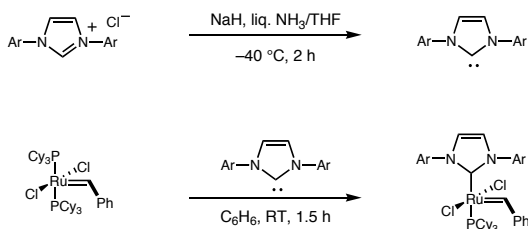
### N-Heterocyclic Carbene Ligands



■ N-heterocyclic carbenes are stronger  $\sigma$ -donors and much less labile than phosphines

■ Herrmann's catalyst does not fit the design motif because the N-heterocyclic ligands do not readily dissociate

Westkamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, 37, 2490.

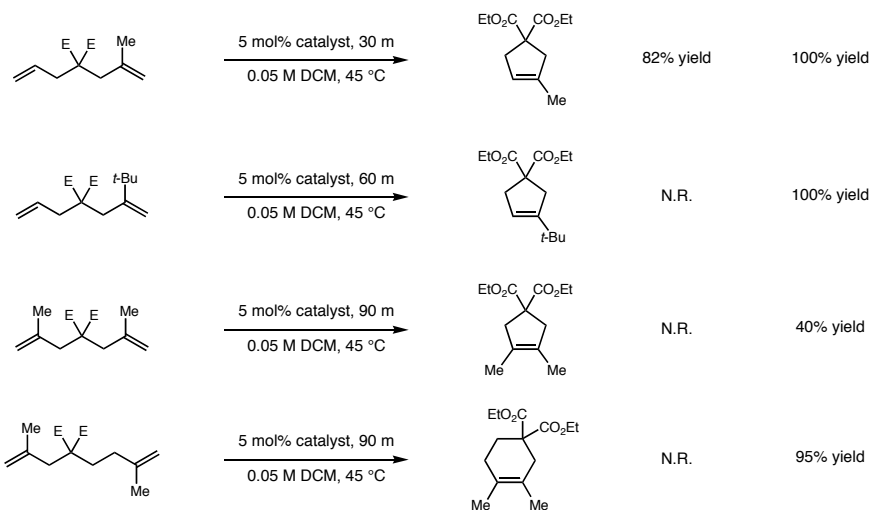
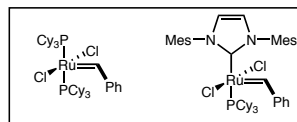


■ A mixed phosphine N-heterocyclic carbene catalyst system should meet the design motif

■ Strong  $\sigma$ -donation of the N-heterocyclic carbene should stabilize metathesis intermediates

Scholl, M.; Trnka, T. M.; Morgan J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, 40, 2247.

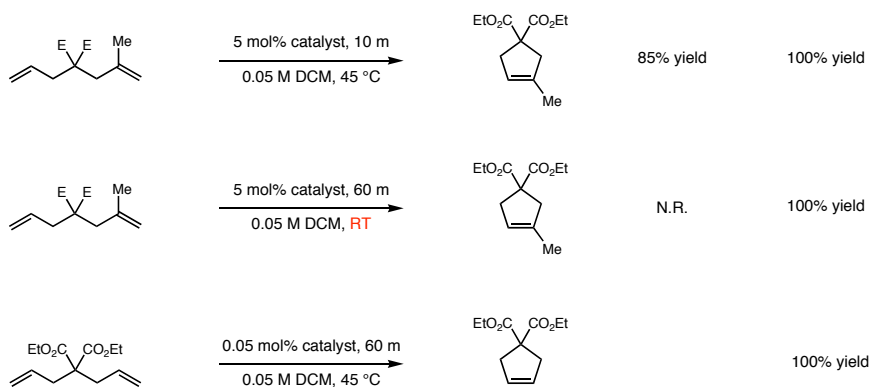
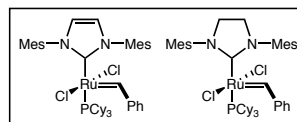
### RCM of Trisubstituted Olefins



■ Dramatic increase in metathesis reactivity with *N*-heterocyclic carbene ligand

Scholl, M.; Trnka, T. M.; Morgan J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, 40, 2247.

### Comparison of *N*-Heterocyclic Carbenes

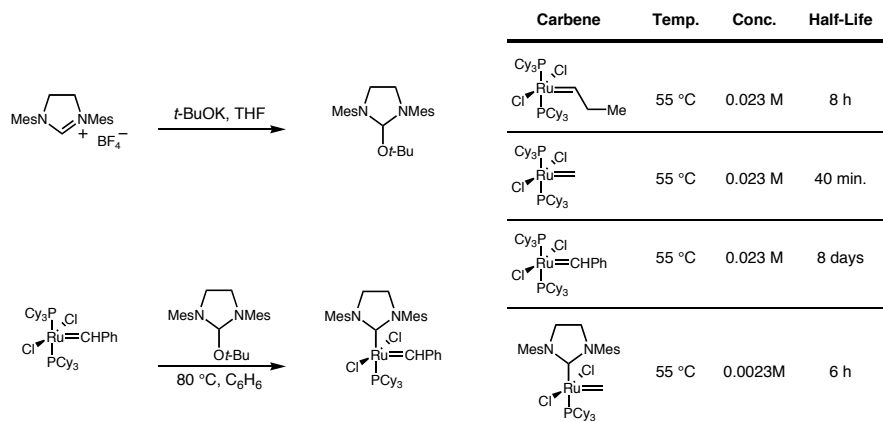


■ Unsaturated *N*-heterocyclic carbene complex requires temperatures above 40 °C

■ Two orders lower catalyst loadings are obtained compared to the bisphosphine ruthenium benzylidene

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

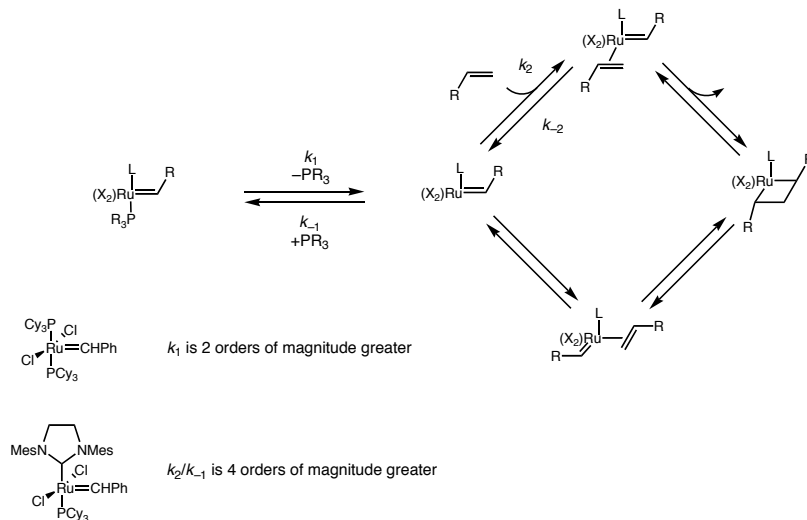
### Decomposition of Ruthenium Carbenes



■ N-Heterocyclic carbene stabilizes ruthenium methylidene leading to longer live catalyst

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

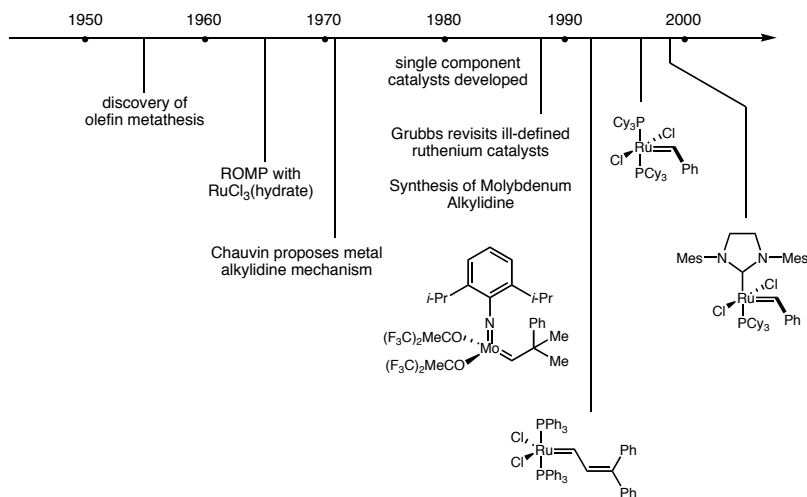
### N-Heterocyclic Carbene Kinetics



■ N-Heterocyclic carbene catalyst can be up to two orders of magnitude faster than biphosphine catalyst

Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, 125, 10103.

### Milestones in Olefin Metathesis



■ Olefin metathesis has progressed from its discovery with ill-defined catalysts systems to the use highly reactive precisely engineered single molecule catalysts

Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.