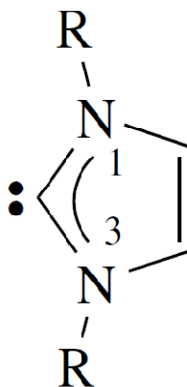
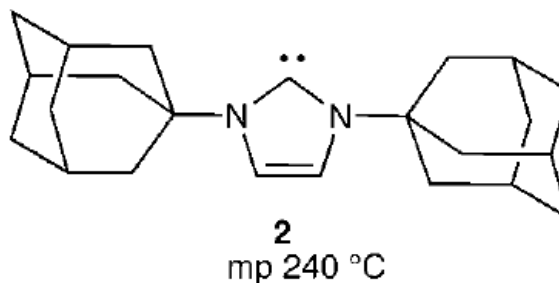
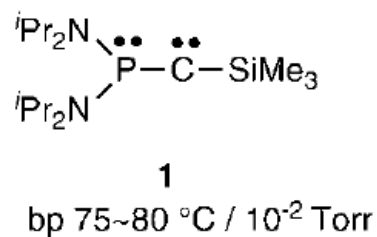
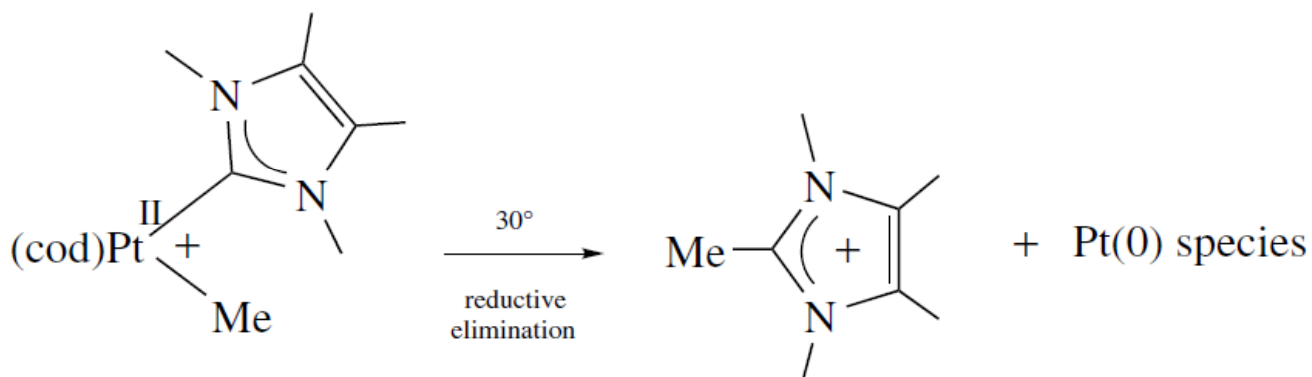


# N-Heterocyclic Carbenes (NHCs)



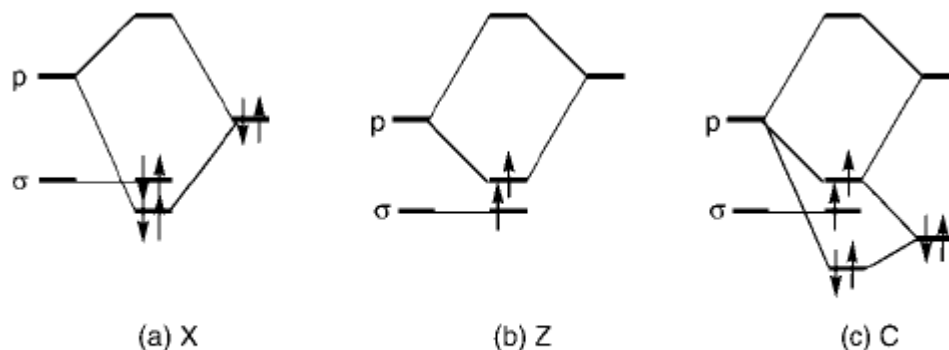
- In contrast to Fischer and Schrock type carbenes NHCs are extremely stable, inert ligands when complexed to a metal centre.
- Similar to phosphine ligands they are ***electronically and sterically tunable***
- Also, like phosphines they are ***very good  $\sigma$ -donors*** and promote a wide variety of catalytic reactions

- NHCs differ from phosphines in two important ways
  - **pro:** The thermodynamic instability of free NHCs strongly disfavours dissociation
  - **con:** Reductive elimination can occur with liberation of the imidazolium salt
- Many catalysts containing NHCs nevertheless are stable for thousands of turnovers so productive chemistry can be much faster than decomposition



- The nature of the R groups at N<sup>1</sup> and N<sup>3</sup> have little influence on the electronic properties of the ligand however are **very important for imparting steric control in a catalyst**.
- Similar to Fischer and Schrock carbenes the NHC ligand binds through an  $sp^2$  hybridized carbon.
- Delocalization of the N<sup>1</sup> and N<sup>3</sup> lone pairs into the empty  $p$  orbital of the carbene carbon **stabilizes the singlet state by > 80 kcalmol<sup>-1</sup> relative to the triplet state**.
- The filled  $sp$  orbital donates  $2e^-$  to the metal centre with the empty  $p$  orbital available for  $\pi$  back donation from the metal centre.
- As this is a Fischer carbene (singlet) type ligand, and especially with the two adjacent filled N-atom  $sp$  orbitals, back bonding is minimal in these ligands and can often be drawn with a single M-C bond.
- This allows rotational freedom about the M-C bond making NHCs less sterically demanding than at first glance.

# Singlet vs. Triplet substituents

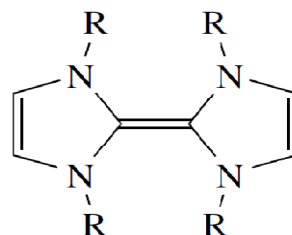


**Figure 2.** A carbene p-orbital interacting with (a) an X substituent, (b) a Z substituent, and (c) a C substituent.

- Substituents interacting with a  $\pi$  system can be roughly classified into three classes, on the basis of the perturbation orbital diagram: namely X ( $\pi$ -electron donors such as  $-\text{NR}_2$ ,  $-\text{OR}$ ,  $-\text{SR}$ ,  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{Br}$ , and  $-\text{I}$ ), Z ( $\pi$ -electron acceptors such as  $-\text{COR}$ ,  $-\text{SOR}$ ,  $-\text{SO}_2\text{R}$ ,  $-\text{NO}$ , and  $-\text{NO}_2$ ), and C (conjugating groups such as alkenes, alkynes, or aryl groups).
- An X substituent, which has a p orbital, or other suitable doubly occupied orbital which will interact with the  $\pi$  bond, raising the vacancy 2p orbital of the carbene, thereby increasing the separation of the 2p and  $\sigma$  ( $\text{sp}^2$ ) orbital. The ground-state of an X-substituted carbene becomes singlet. Many carbenes in this class are known, e.g alkoxy or halo carbenes.
- Z substituents having a p or  $\pi^*$  orbital and C substituents having evenly spaced  $\pi$  and  $\pi^*$  orbitals, respectively, either lower the 2p– $\sigma$  ( $\text{sp}^2$ ) gap or leave it about the same as shown in Figure 2(b) and (c). In either case, the groundstate for these carbenes is expected to be triplet although the magnitude of  $\Delta G_{\text{ST}}$  may vary. It has been demonstrated by ESR studies that most aryl and diarylcarbenes have triplet ground states.

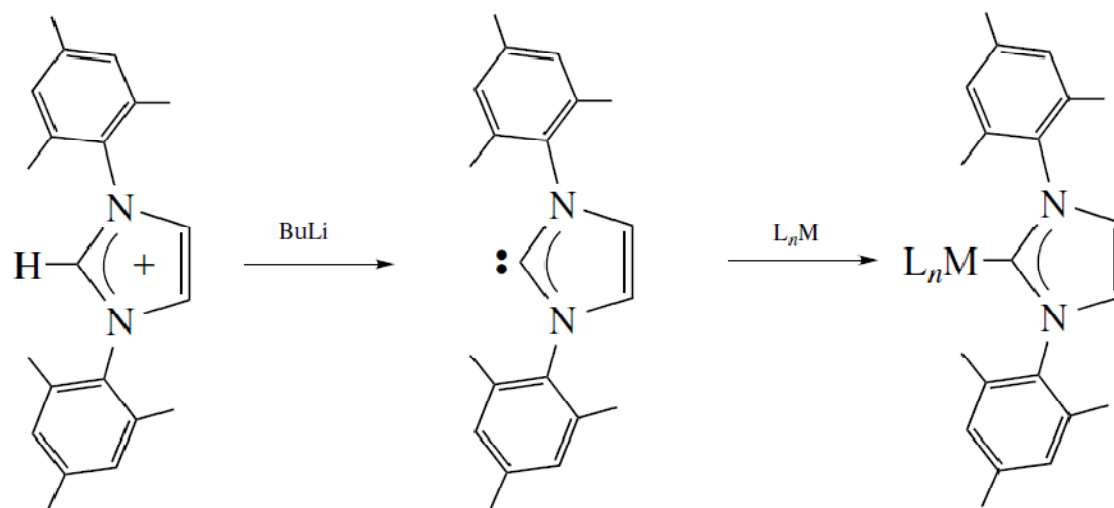
# Synthesis

- NHCs were first prepared in 1968 by Ofele, Wanzlick and Schonherr.
- In the 1970's Lappert reported a series of complexes via cleavage of the electron rich olefin

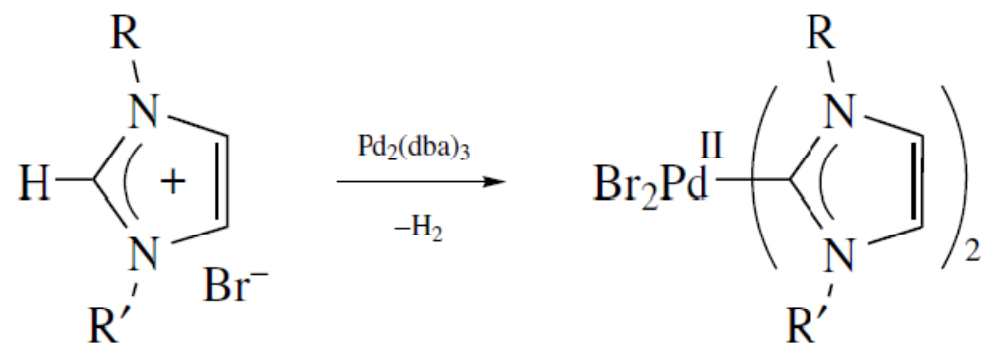


- Alternatively prepared via deprotonation of the imidazolium salt

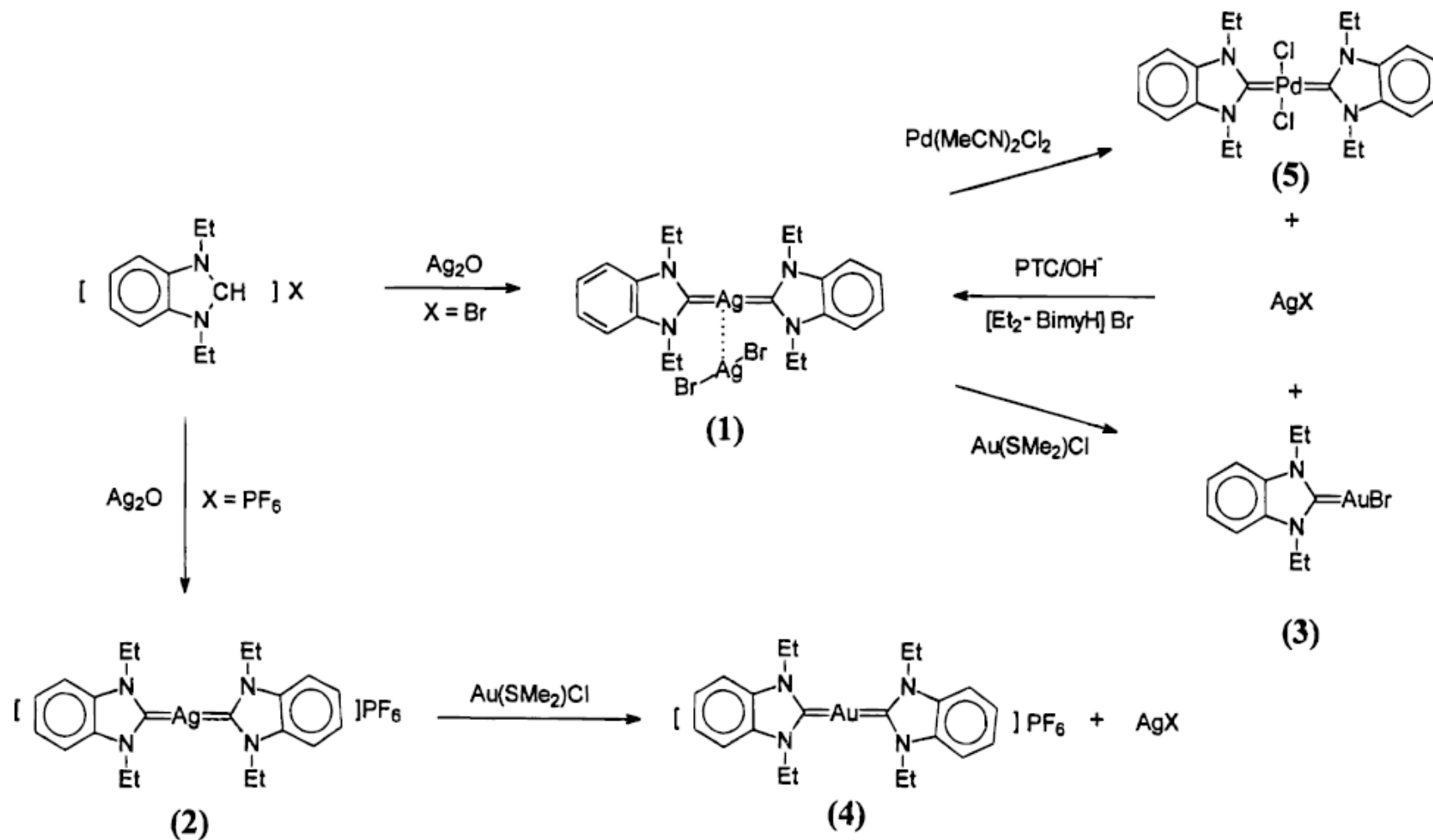
This requires the presence of bulky R groups, e.g. mesityl, to impart transient stability to the free NHC and preclude abstraction of any other acidic protons.



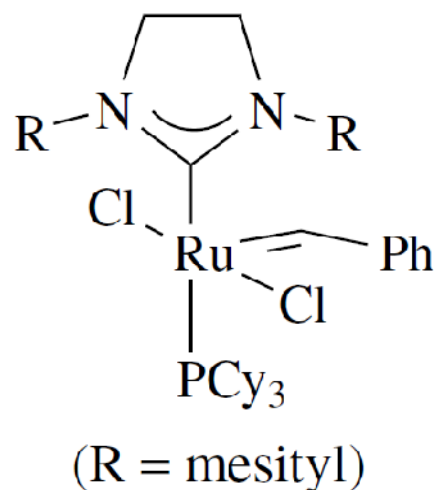
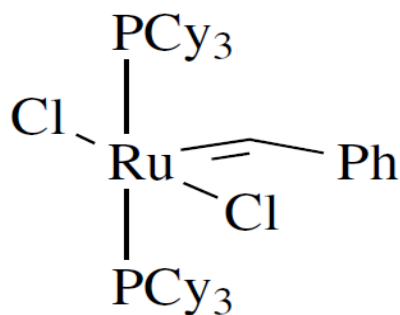
- Milder routes have been developed for more sensitive NHCs
- Oxidative addition being the simplest, however, the product may undergo further reaction.



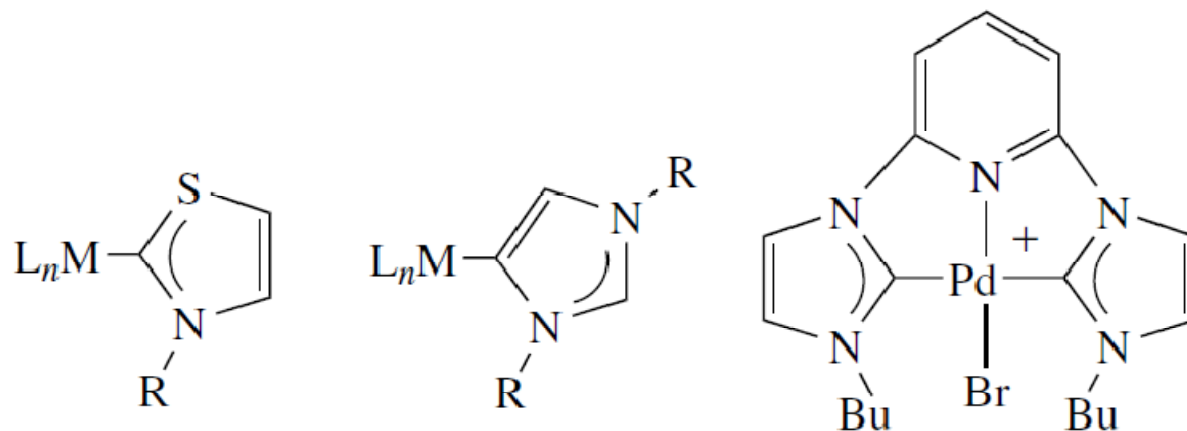
- A commonly employed method is that developed by Lin et al. where AgO is converted to a Ag(I) NHC stable intermediate which readily undergoes transmetalation.



- From 1994 Hermann began to develop NHCs as spectator ligands in homogeneous catalytic systems
- The most celebrated use of NHCs however is their application in Grubb's catalyst.
- Replacement of a  $\text{PCy}_3$  ligand by a NHC ligand increased the TOF by 3 orders of magnitude
- Attributed to the high *trans*-effect of the NHC labilizing the remaining  $\text{PCy}_3$  ligand, i.e. opening a catalytic site for substrate activation



- There are numerous catalytic applications of NHCs in which they can have advantages over phosphine ligands (hydrogenation, hydrosilation, metathesis, C-C coupling, etc.)
- Rates can be faster and catalysts may be air stable
- Imidazoles are also more readily synthesized and functionalized.
- M-C bond formation is always trickier for NHCs however relative to phosphines.
- Synthetic variations of NHCs are becoming more common

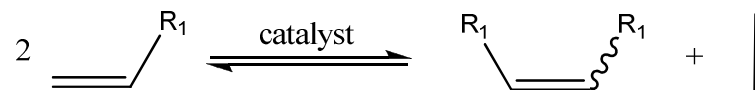


# Alkene and Alkyne Metathesis

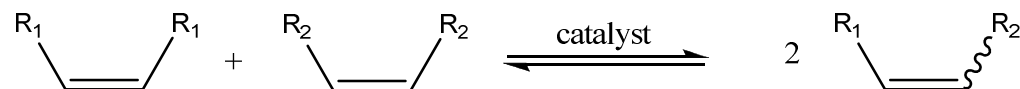
- Metathesis; derived from the Greek word meaning “to place differently” or “to transpose” is so general that it comes to a close definition of synthetic chemistry.
- In the narrower sense it is here referred to as describing the metal-catalyzed exchange of alkylidene and alkylidyne units in alkenes and alkynes, respectively.
- A simple example is the conversion of propene into ethene and 2-butene (Phillips tri-olefin process)



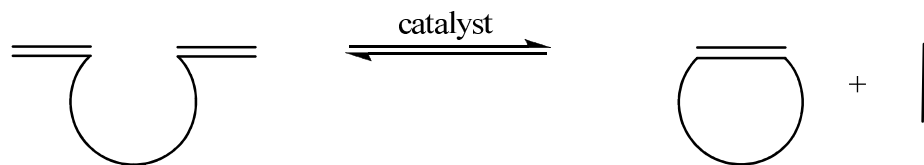
# Alkene Metathesis



**SM** self-metathesis

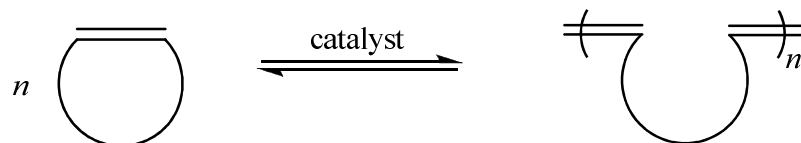


**CM** cross-metathesis

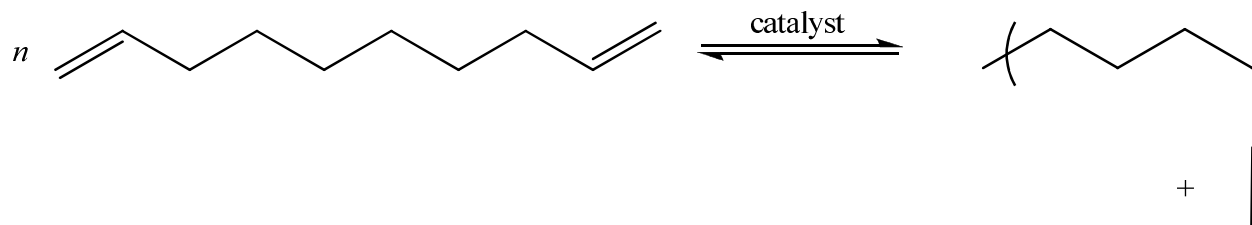


**RCM** ring closing metathesis

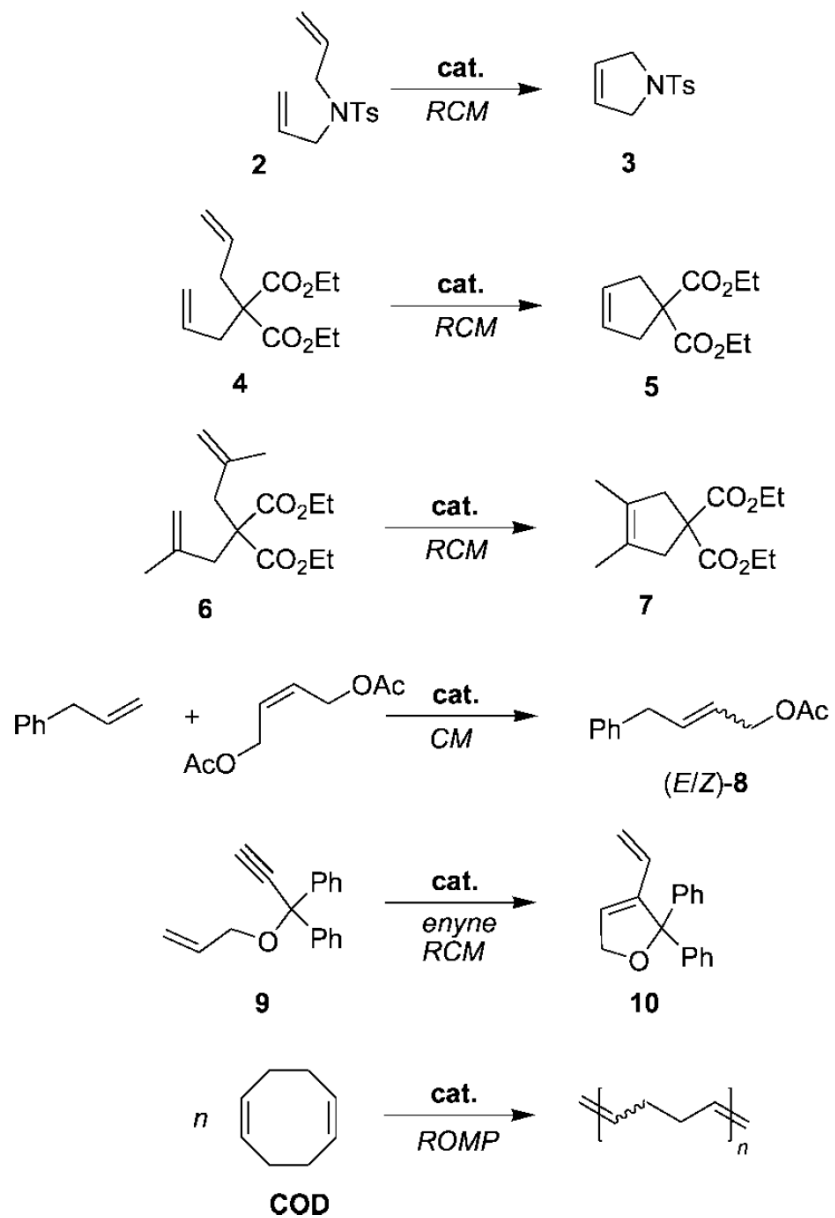
**ROM** ring opening metathesis



**ROMP** ring opening metathesis polymerization

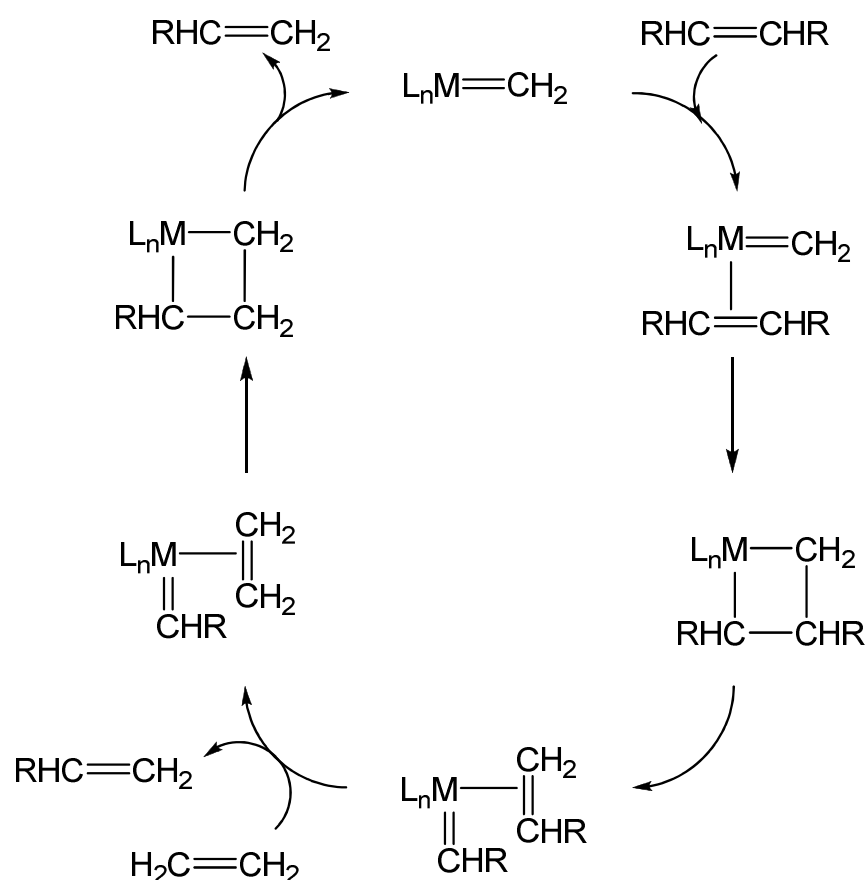


**ADMET** acyclic diene metathesis polymerization



Benchmark transition metal catalyzed metathesis transformations

- Alkene metathesis are almost thermoneutral equilibria and a shift in the desired direction is often achieved by the removal of a volatile component (e.g. ethylene)
- The mechanism of alkene metathesis generally recognized today was first postulated in 1970 by Chauvin, and later proved by Schrock in 1989 with the isolation and structural characterization of the metallacyclobutane intermediate.



Chauvin Y. Macromol. **1970**,161.

Schrock R. R. Organometallics **1989**, 8, 2260.

- A metal carbene unit  $L_nM=CH_2$  thus functions as the catalytically active center.
- Mo, W, Re and Ru metal centers have proven to be particularly with respect to alkene metathesis catalysis.
- Initial metathesis catalysts were derived from transition-metal halides and carbanion donors, e.g.  $WCl_6$  /  $Et_2AlCl$  /  $EtOH$  , which are thought to form metal carbene catalysts in-situ via  $\alpha$ -elimination.
- Today well designed and fully characterized catalysts are used on an industrial scale.



# The Nobel Prize in Chemistry 2005



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## Press Release

5 October 2005

[The Royal Swedish Academy of Sciences](#) has decided to award the Nobel Prize in Chemistry for 2005 jointly to

**Yves Chauvin**

Institut Français du Pétrole, Rueil-Malmaison, France,

**Robert H. Grubbs**

California Institute of Technology (Caltech), Pasadena, CA, USA and

**Richard R. Schrock**

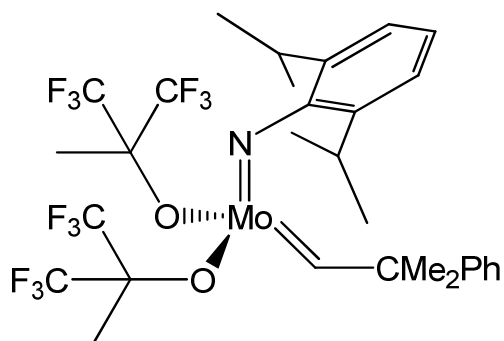
Massachusetts Institute of Technology (MIT), Cambridge, MA, USA

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

## Metathesis – a change-your-partners dance

[http://nobelprize.org/nobel\\_prizes/chemistry/laureates/2005/press.html](http://nobelprize.org/nobel_prizes/chemistry/laureates/2005/press.html)

- Both Schrock and Grubbs type alkene metathesis catalysts have a low coordination number  $CN = 4$  (after dissociation of  $PCy_3$  by Grubbs catalyst)
- This allows facile access of the alkene to the central metal centre, where the decisive coordination step occurs.
- Spectator ligands such as imido or oxo functions commonly found in metathesis catalysts promote formation of the metallacyclic intermediates.



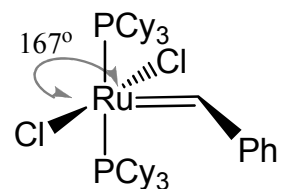
**Schrock (1990)**

Highly reactive

Poor tolerance of functional groups in substrate

The catalytic activity increases with the electron withdrawing nature of the two alkoxy ligands

Metathesis of tri- and tetra-substituted olefins is possible

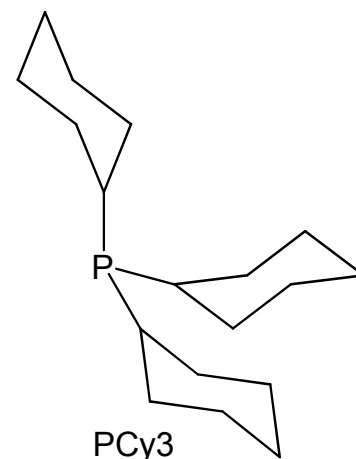


**Grubbs (1995)**

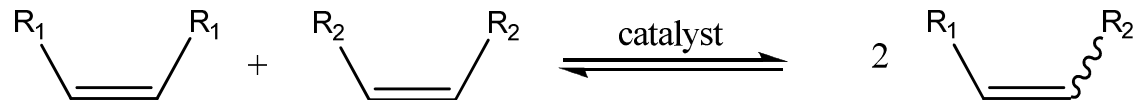
Tolerance of functional groups in substrate  
(CO, OH, NH)

Selectivity towards sterically unhindered olefins  
and strained olefins

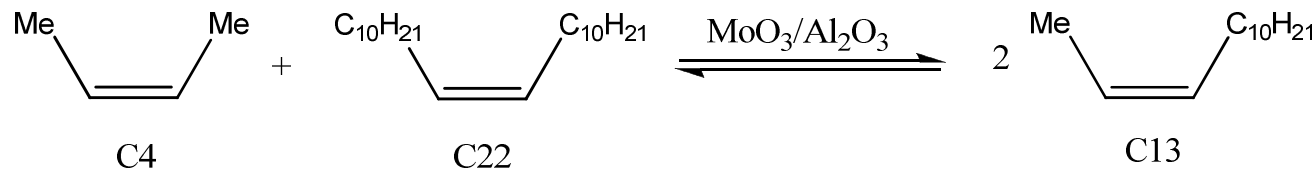
Tri- and tetra-substituted olefins are not attacked



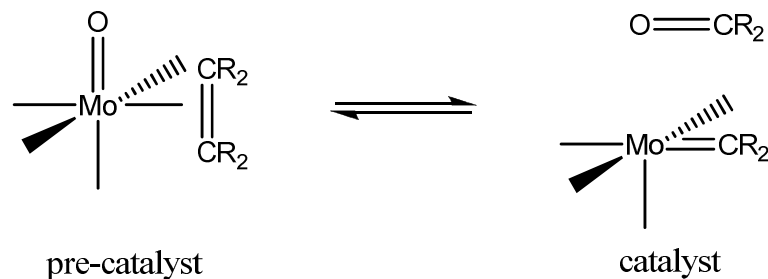
# Cross Metathesis (CM)



- Cross metathesis has been used in industry in the form of the Shell higher olefin process (SHOP) since 1977.
- This process is a combination of oligomerization, isomerization, and metathesis steps.



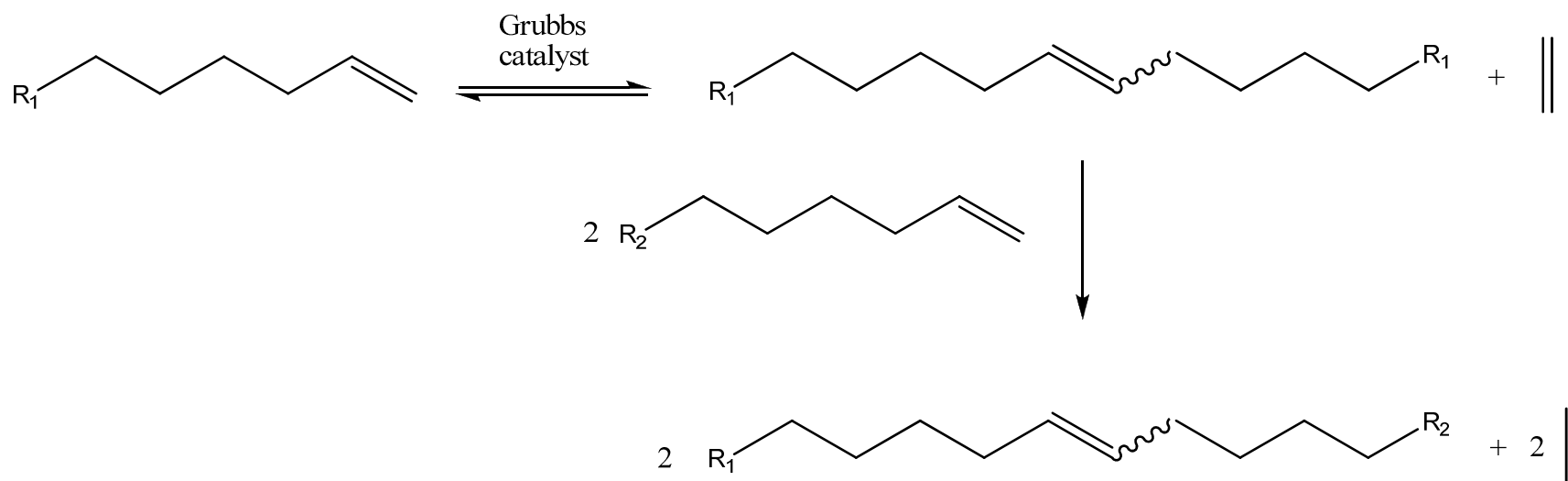
- First, linear  $C_4$  to  $C_{30+}$   $\alpha$ -olefin chains are produced from ethylene. Enrichment of the  $C_8 - C_{18}$  fraction, which is of interest for application in various productions, is possible by a heterogeneous cross-metathesis reaction.



- Cross metathesis has only found limited applications however due to product “branching”.

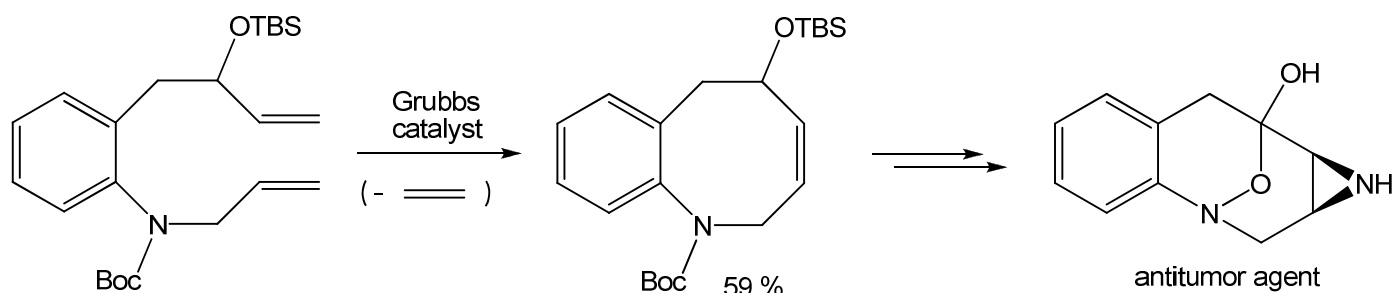


- Grubbs reported that heterodimers are obtained in high yield when one of the starting olefins first undergoes homodimerization.

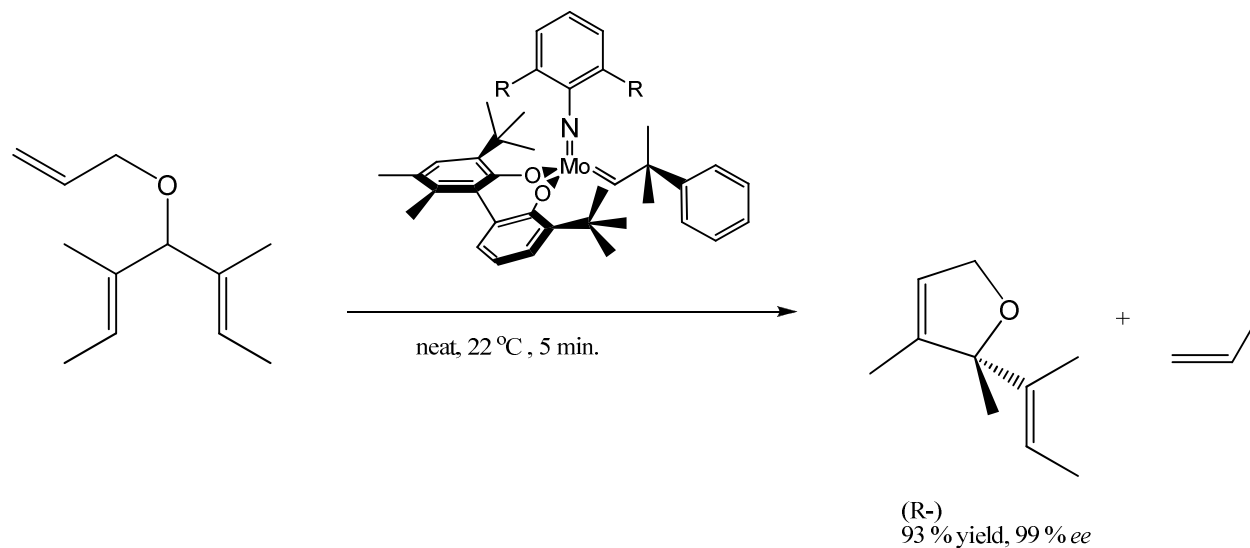


# Ring Closing Metathesis (RCM)

- Ring closing metathesis is today considered a standard method in any organic synthesis laboratory (high dilution is required for diffusion controlled RCM to avoid CM).
- Its suitability for the preparation of N-heterocycles has inspired natural product synthesis.

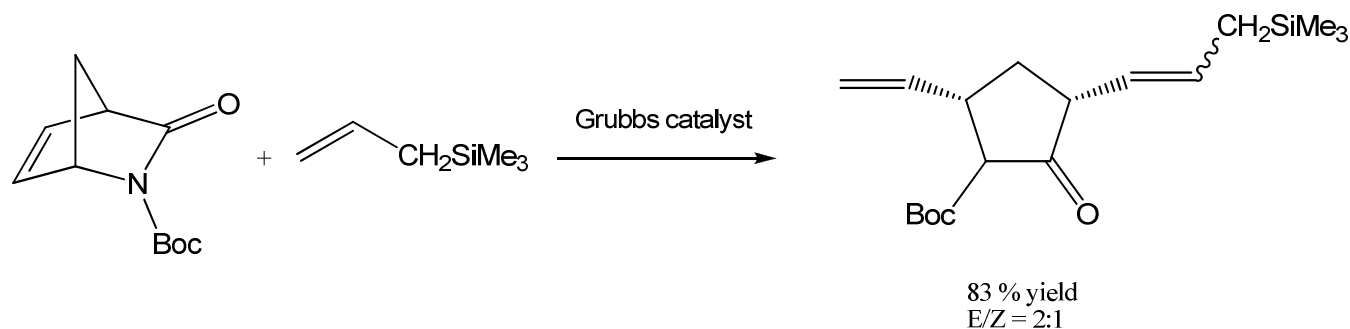
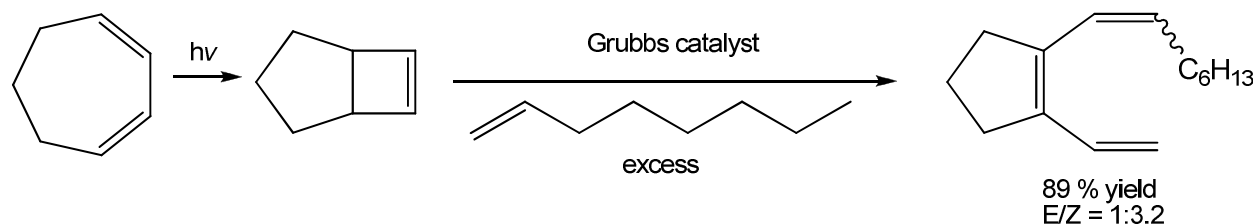


- Asymmetric ring closing metathesis (ARCM) has also been developed.



# Ring Opening Metathesis (ROM)

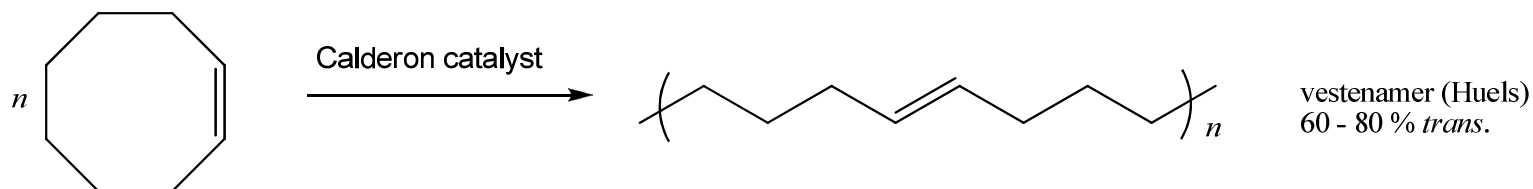
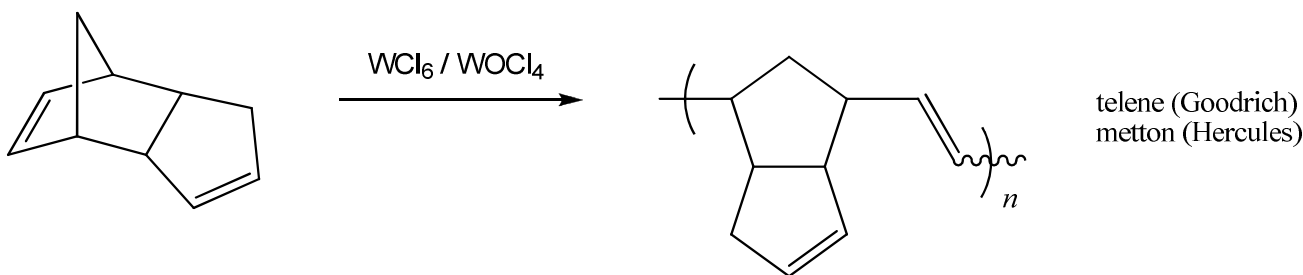
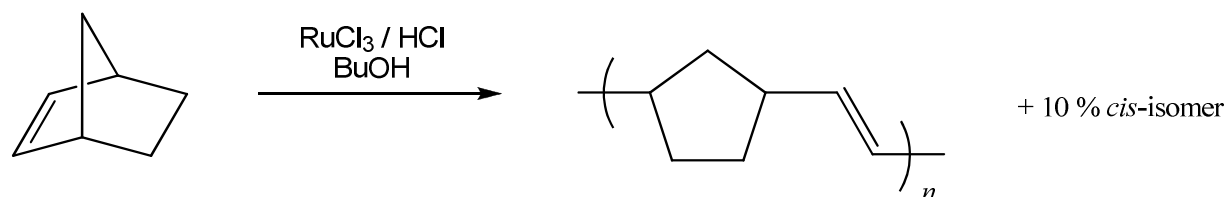
- Ring opening metathesis is the reversal of ring closing metathesis.
- ROM is applied as a cross-metathesis in the presence of ethylene and is in principle suitable for the preparation of terminal dienes.
- Ring strain favors ring opening, and thus ROM processes are especially common with norbornenes and cyclobutenes.



- High dilution and excess  $\alpha$ -alkene largely suppresses the self-metathesis of the cycloalkane.
- Synthetic utility is limited by the formation of different cross-metathesis and self-metathesis products, however, in some cases selectivity can be controlled.

# Ring Opening Metathesis Polymerization (ROMP)

- Whereas in ROM the self metathesis is suppressed, this process is desired in ROMP thus the use of open-chain alkene substrates is avoided.
- ROMP has been used industrially since 1976:

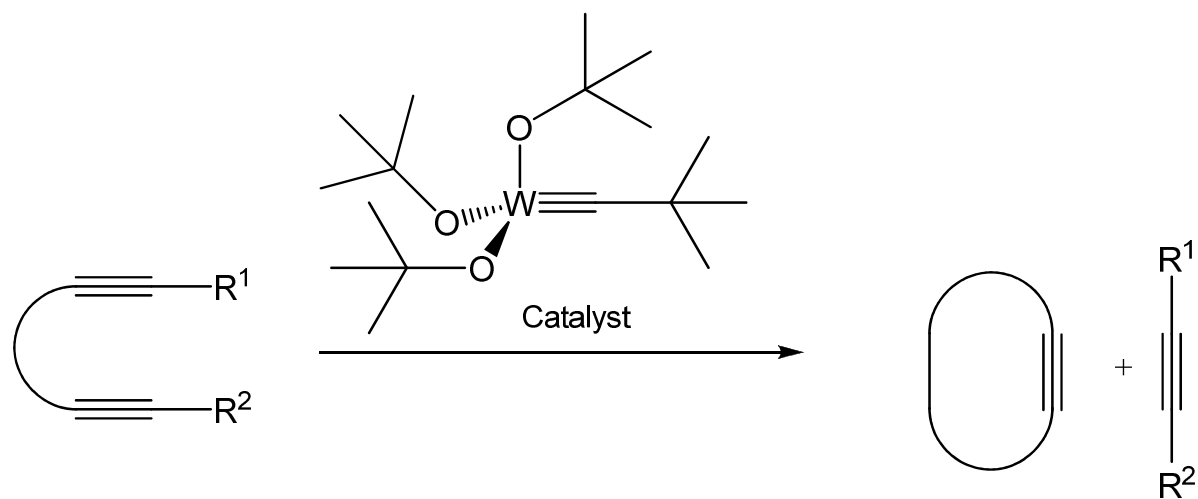


- The C=C bonds allow for cross-linking (vulcanization) following ROMP.

- ROMP processes are unique in that the C=C double bond of the monomer is conserved in the polymer.
- The catalytically active species is fixed to the end of the growing chain (aka living polymer).
- As soon as a certain monomer is consumed, the chain reaction can be continued with a different monomer (block co-polymerization).
- A  $L_nM=CR_2$  unit can be deactivated by a reaction with a carbonyl group to yield a metal oxide allowing narrow molar-mass distributions to be achieved.

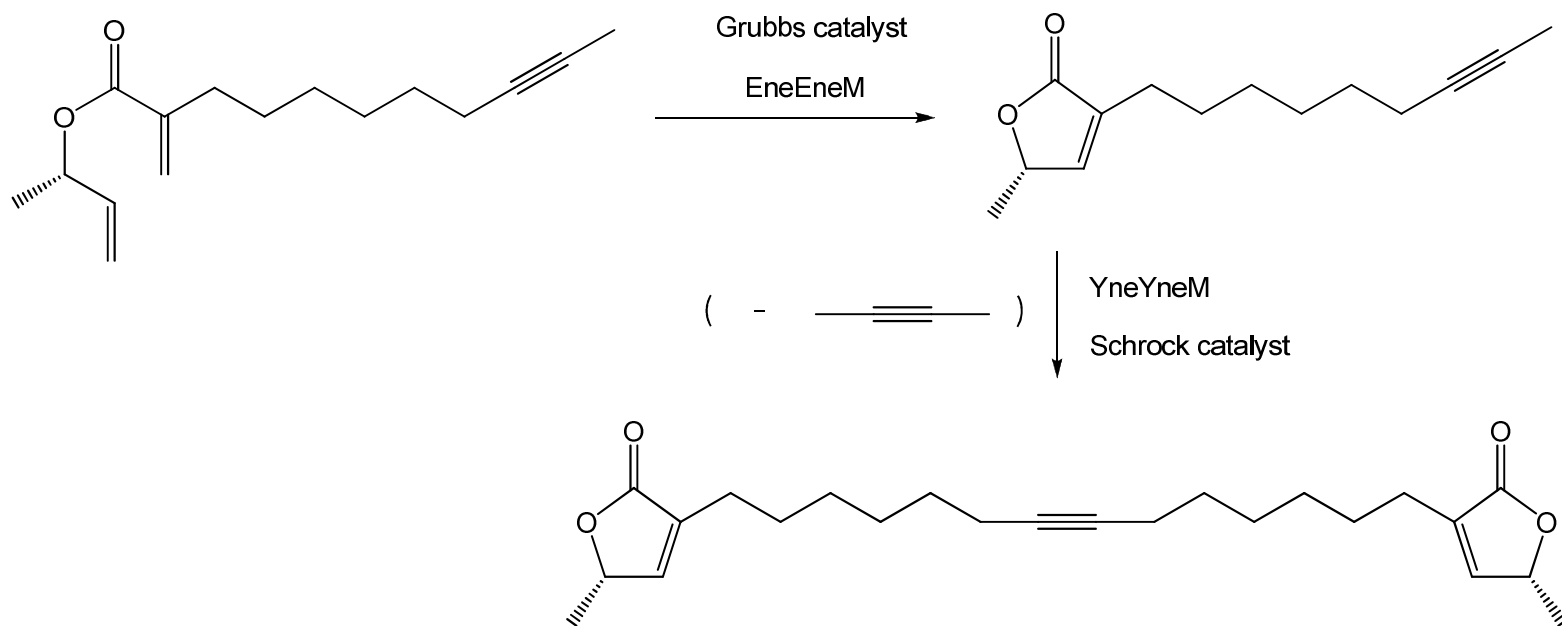
# Alkyne Metathesis

- Metathesis involving  $\text{C}\equiv\text{C}$  triple bonds can proceed symmetrically (YneYneM) and in the mixed form (EneYneM).
- The ring closing metathesis of two alkynes (YneYneRCM) under high dilution conditions leads to a cycloalkyne and (preferentially) a volatile open alkyne.



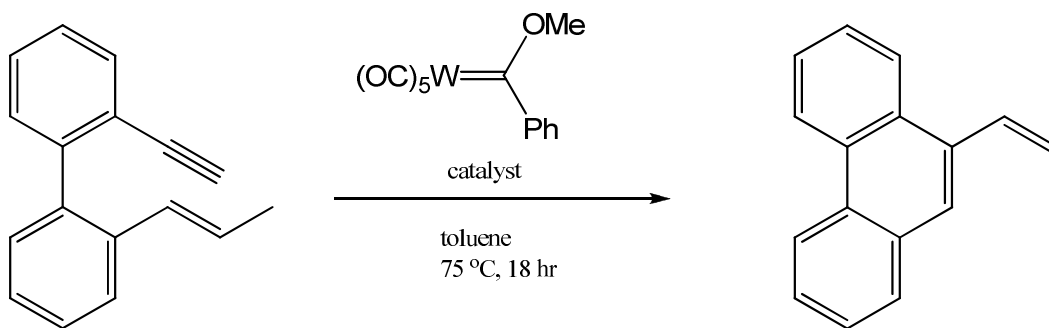
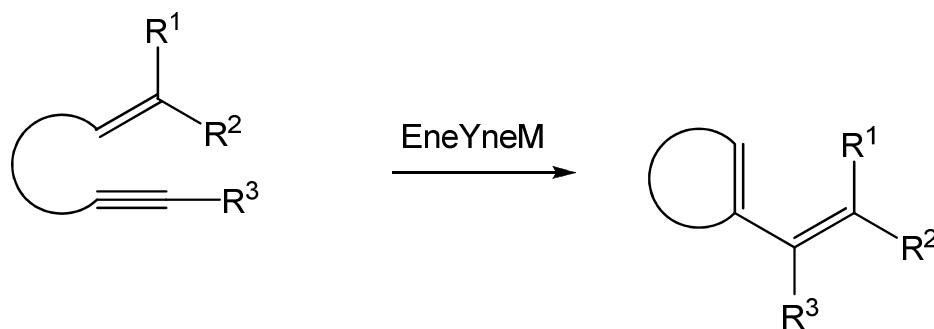
# Alkyne Metathesis

- The presence of C=C double and C≡C triple bonds in the reactants presents two kinds of challenges:
  - selective metathesis with the formation of only one bond type (EneEneM, YneYneM)
  - the participation of both structural elements (EneYneM)
- This competition can be controlled by careful choice of catalyst.

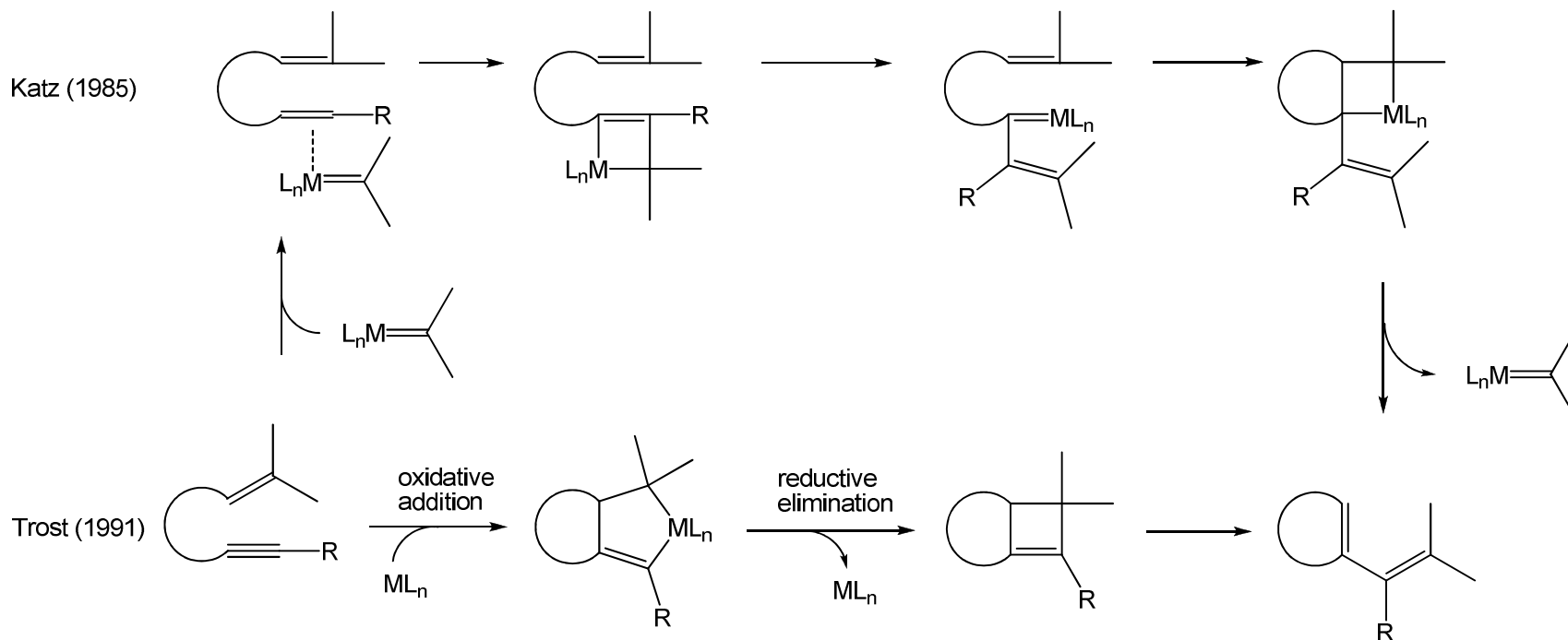


# Alkene-Alkyne Metathesis

- Mixed enyne metathesis (EneYneM) have been know to occur

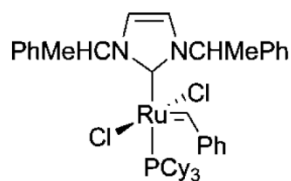


- A special feature of the alkene-alkyne metathesis is its “atom economy” as all carbon atoms remain in the product.
- In addition, a butadiene moiety is formed in the product which is suitable for further functionalization (e.g. Diels-Alder reaction).
- Two mechanisms have been proposed; the reaction pathway being determined by the nature of the substrate and the catalyst.



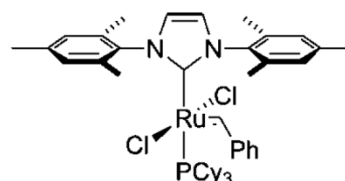
# Modern Grubbs catalysts

- Mindful of the stabilizing effect of NHC ligands, the groups of Nolan, Grubbs, and Fuerstner and Herrmann, independently and almost simultaneously proposed the idea of combining a labile phosphine group for rapid metathesis initiation with a non-labile NHC ligand.
- The resulting mixed phosphine/NHC complexes, **proved to be superior** to the bis(NHC) and bis(phosphine) complexes in overall metathesis activity.



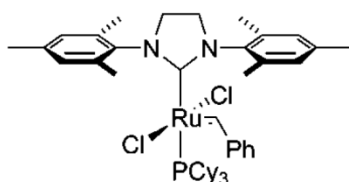
**15**

Fürstner and Herrmann, **1999**



**16**

Nolan, Grubbs, **1999**



**17**

Grubbs, **1999**

## Mechanism of Metathesis Catalyzed by Common Ru Precatalysts

