Grubbs Metathesis

Introduction

What is metathesis?

In metathesis reactions, double bonds between carbon atoms are broken and reformed in a way that causes atom groups to change places.

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are needed to see this picture.

Meta = change
Tithemi = place

Metathesis applications

- Metathesis reactions do not occur in nature, but are convenient “short cuts” in organic synthesis.
- Therefore, they can be used for:
  - Insecticides
  - Pharmaceticals
  - Foodstuffs
  - Chemical industry
  - Biochemical technology
  - Polymers
  - Paper industry

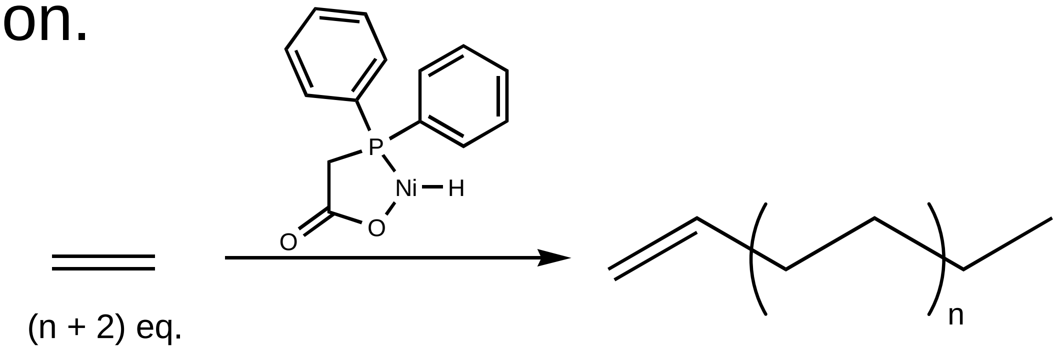
Before Grubbs

SHOP Process

- Industrial scale production process
- Produces linear high olefins starting from ethene.
  - Yields a mixture of even numbered olefins with between 4 to 40 carbons in the chain.
- This process is commonly used industrially.
  - Petrochemical industry, polymers, and specialty chemicals.

SHOP Process

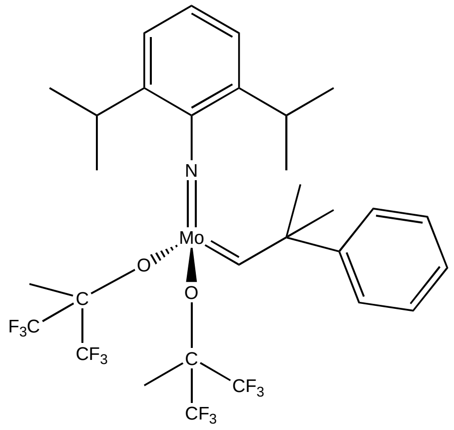
- Ethene is first oligomerized in the presence of a homogeneous nickel-phosphine catalyst.
  - Reaction conditions include a polar solvent (1,4-butanediol), 90-100˚C, and 100-110 bar.
- In the second step the alkenes undergo double bond isomerization using a solid potassium metal catalyst which gives a mixture of internal alkenes.
- In the third step an alumina-supported molybdenum metathesis catalyst resulting in linear internal alkenes from cross-metathesis.
- The produced alkenes are then separated through a distillation.



Competing Reactions

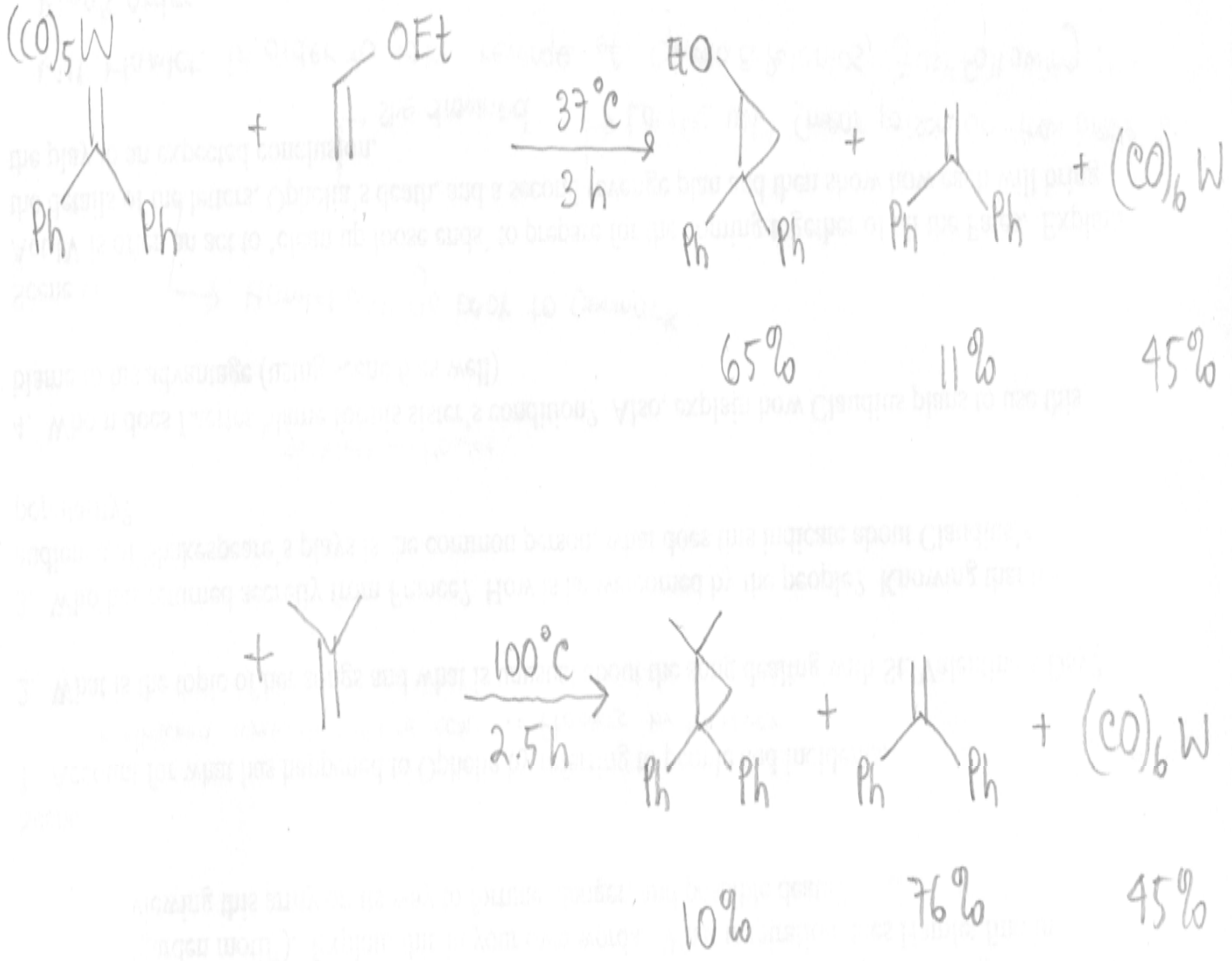
Schrock Catalyst

- This is the main competitor with the Grubbs catalyzed reaction.
- Uses a molybdenum catalyst, which shows greater reactivity than the first generation Grubbs catalyst, particularly with sterically demanding and electron deficient olefins.
- Schrock catalyst has been less commonly used since the development of the second generation Grubbs catalyst.



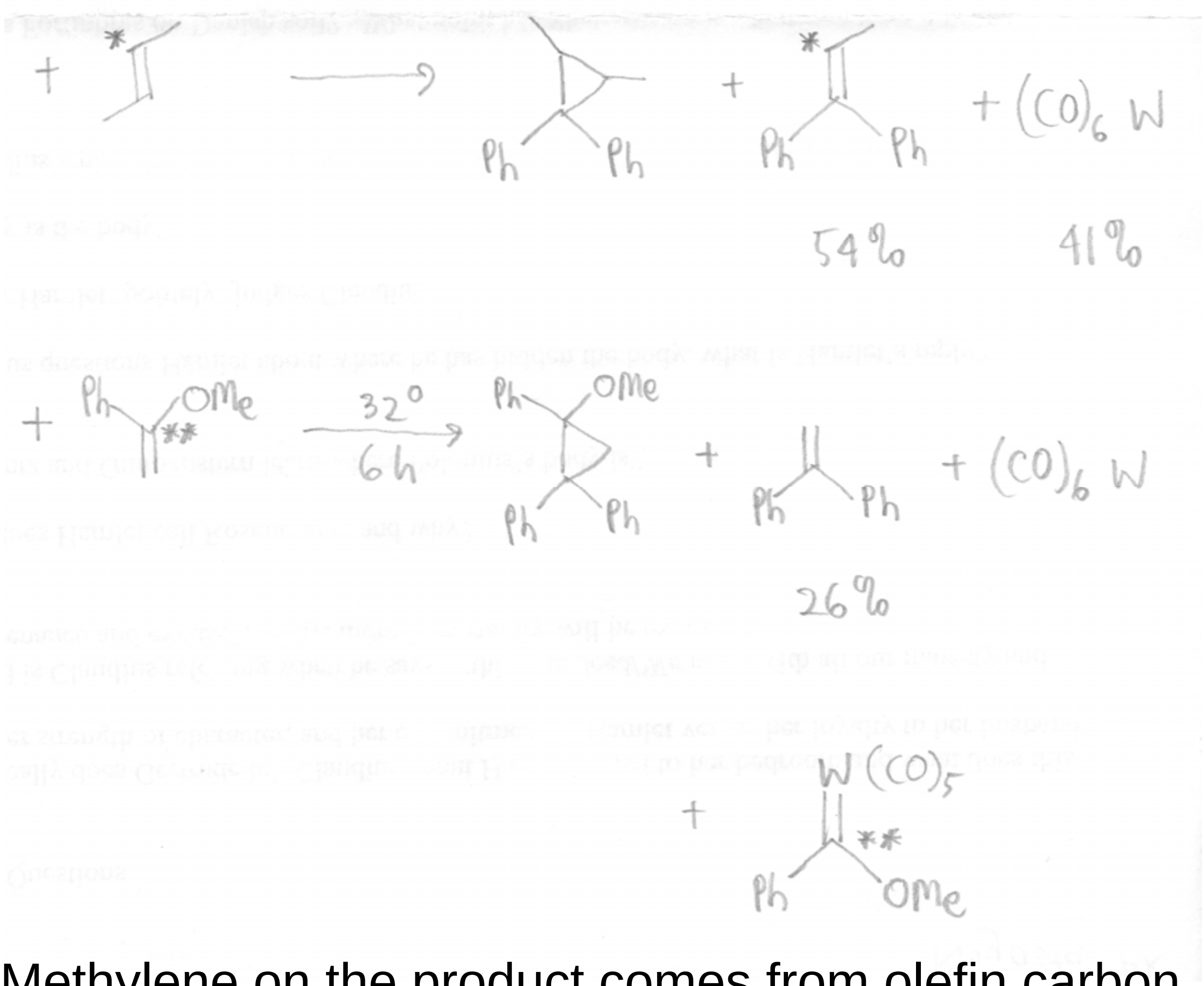
Mechanism

Mechanism: Experiment



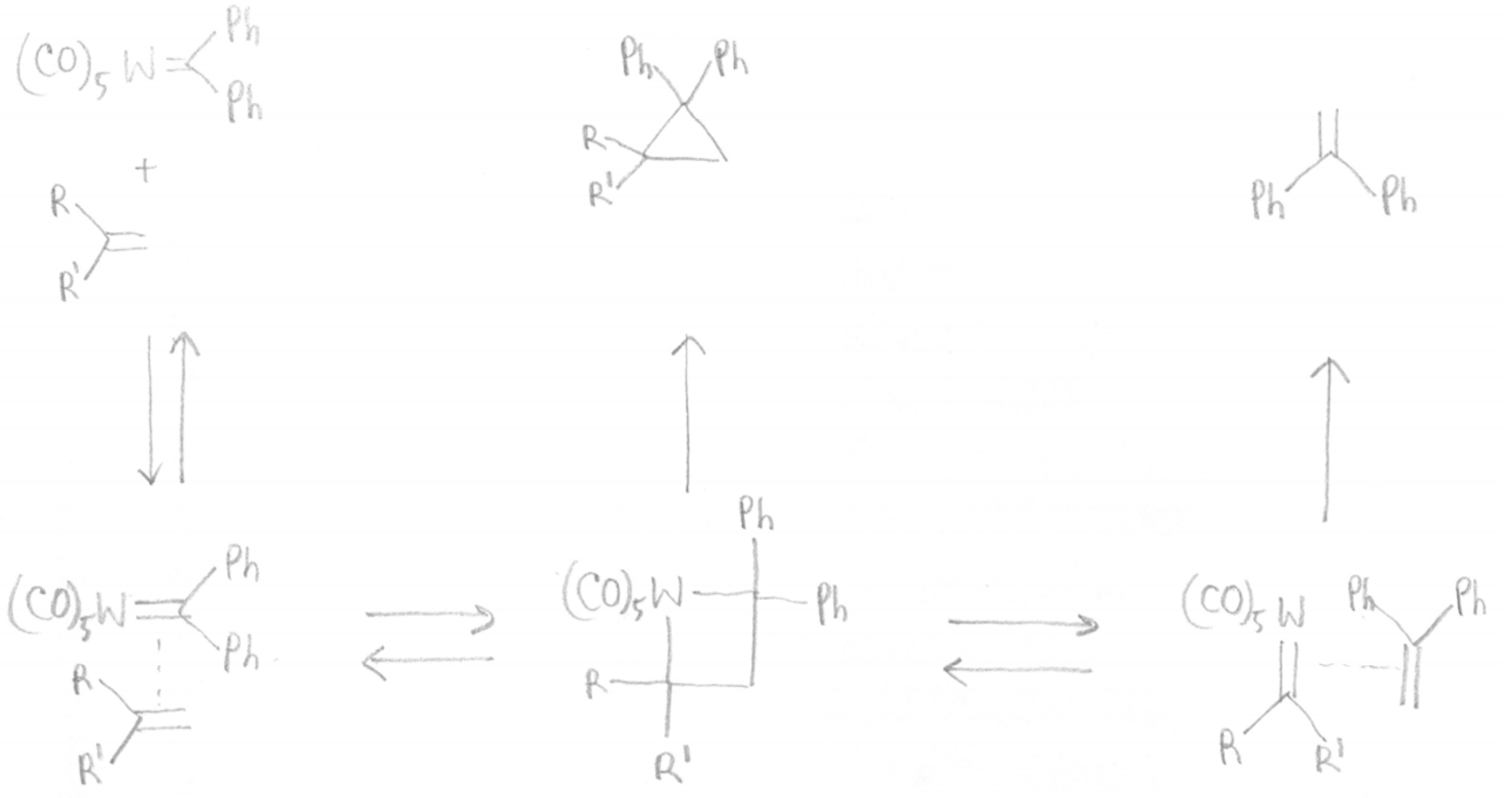
- Cyclopropane → carbene intermidiate

Mechanism: Experiment



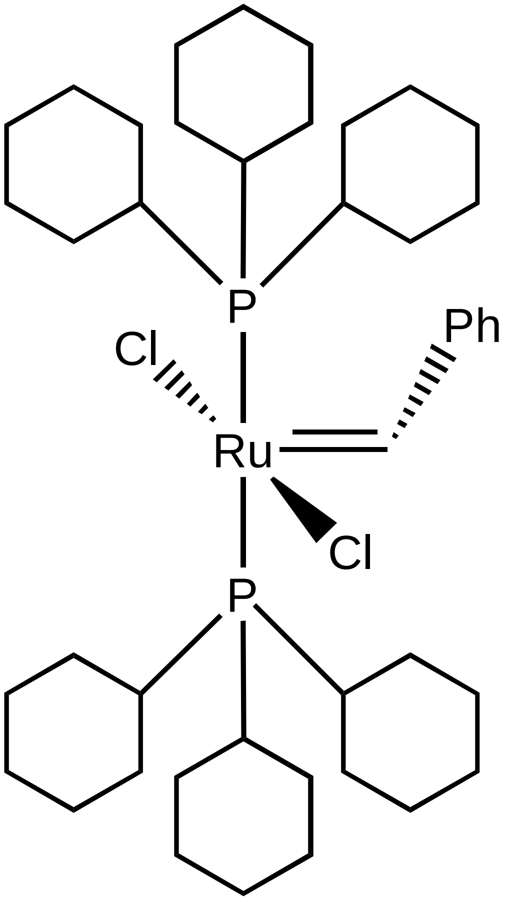
- Methylene on the product comes from olefin carbon.
- Other olefin carbon bonded to metal complex.

Proposed Mechanism



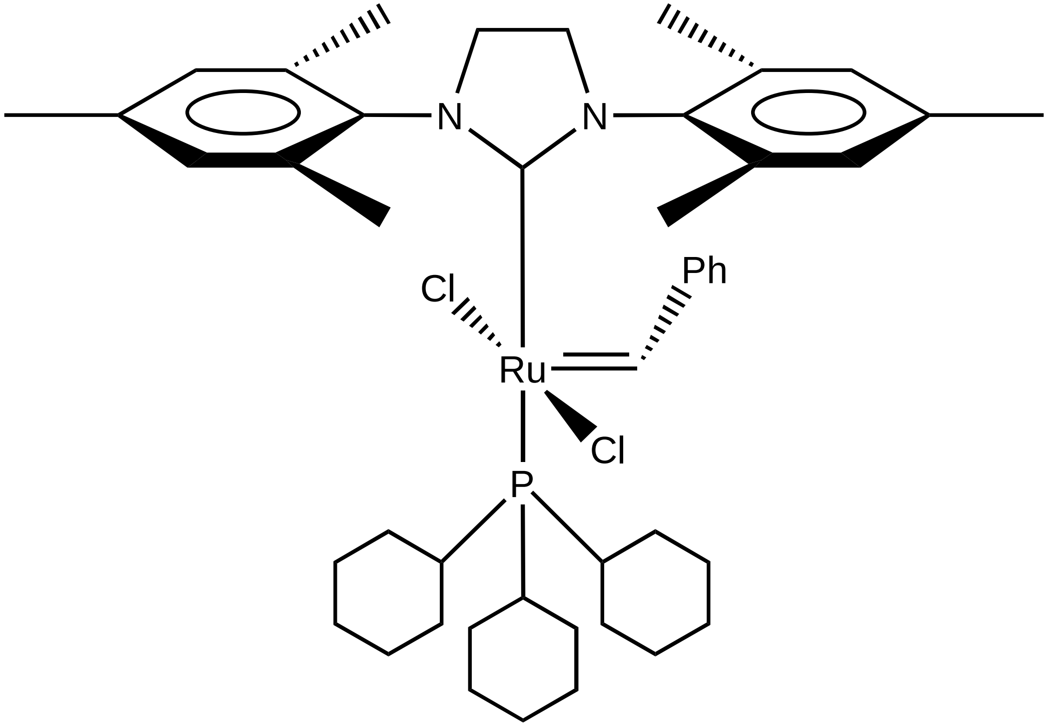
Catalysts

First generation catalyst



Ruthenium-based complexes have good functional group compatibility.

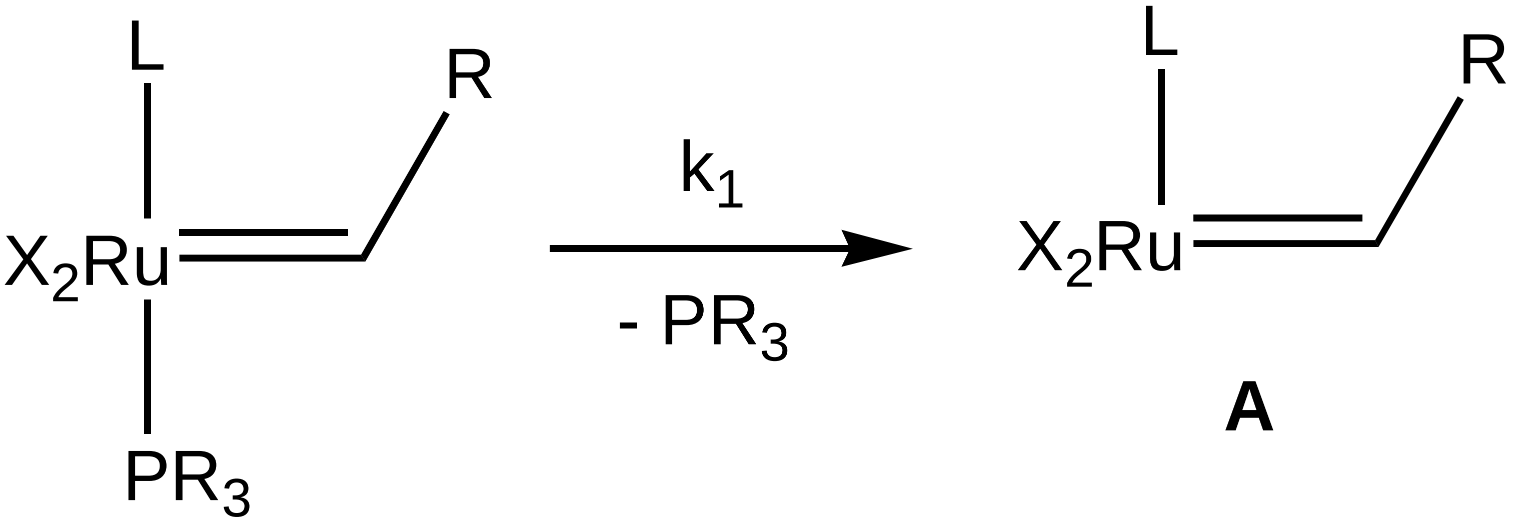
Second generation catalyst



Ruthenium catalysts with N-heterocyclic carbene (NHC) ligands are more reactive than the first generation catalyst, but maintain the high functional group tolerance and air and moisture stability.

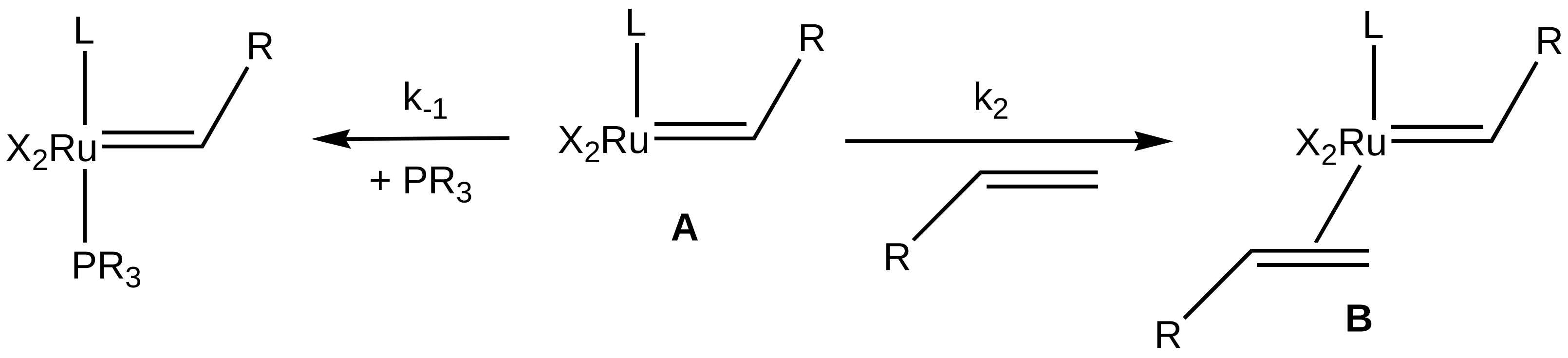
Initiation

- A complex enters the catalytic cycle (initiates) by loss of phosphine with a first order rate constant, k_1, to produce a 14 electron intermediate (A).



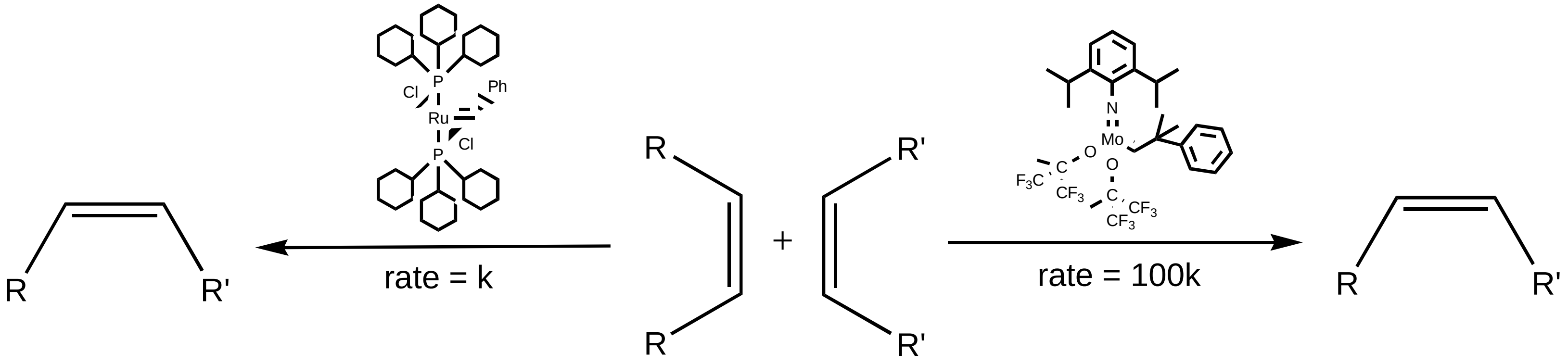
Propagation

- Compound A can then either rebind phosphine (k_{-1}) or bind the olefin (k_2).
  - Rebinding phosphine ends the catalytic cycle.
  - Binding olefin propagates the catalytic cycle.
- Therefore, A is the propagating species.



Relative reactivity

- The ratio of k_{-1}/k_2 is used to measure the extent to which a catalyst prefers to remain in the catalytic cycle.
  - This ratio is 4 orders of magnitude larger for Ru catalysts than Mo catalysts.
  - But the initiation of Ru catalysts is 2 orders of magnitude greater than Mo catalysts.
  - Therefore, metathesis with Mo catalysts is only 2 orders of magnitude faster than with Ru catalysts.



Increasing rate & efficiency

- Increased initiation would permit lower catalyst loadings and reaction temperatures and improve efficiency.

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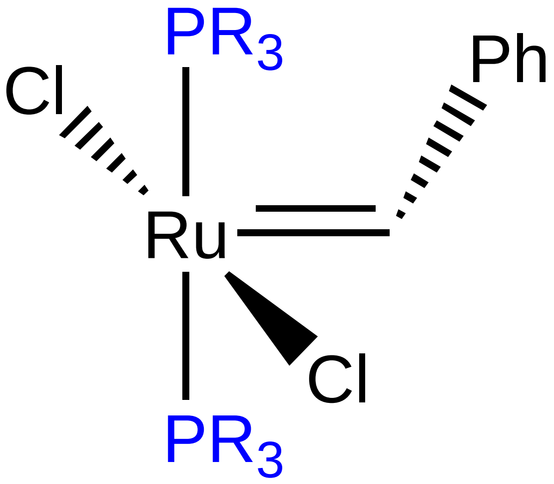
Increasing rate & efficiency

- Initiation (and relative reactivity) can be increased by:
  - Addition of phosphine scavengers (HCl, CuCl). However, these additives limit catalyst lifetime and functional group tolerance.
  - Changing the phosphine group in the catalyst complex. This effects the phosphine dissociation and rebinding without effecting the ligand-olefin reaction.

Phosphine groups

- Experiments showed that in general aryl phosphine dissociation is considerably faster than alkyl phosphine dissociation.
- Therefore, the initiation rates and relative reactivity of several aryl phosphines were measured.



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New catalysts

- All of these catalysts can be prepared in two high yield steps from commercially available reagents.
- However, preparing them is still not as easy as buying pre-prepared catalysts and Sigma-Aldrich does not yet produce them.
- However, it likely soon will.

Cross Metathesis (CM)

Past reactions

- Historically, metathesis was used primarily for ring-opening metathesis polymerizations (ROMP) and ring-closing metathesis (RCM) because:
  - Catalyst activity was too low to effect a reaction without a strong enthalpic driving force (ring-strain release in ROMP or entropic advantage of intramolecular reactions for RCM).
  - Product selectivity was low for the CM products.
  - Stereoselectivity was poor in the newly formed olefin.

Analyzing reactants

- The Grubbs group categorized reactants by their reactivity (represented by their rate of homodimerization) and divided them into 4 categories.

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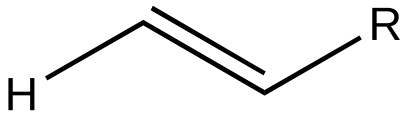
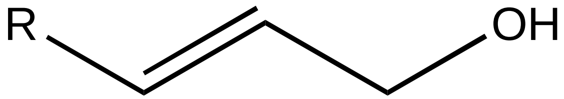
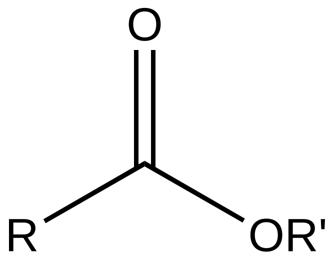
Type I - Fast homodimerization

- Olefins that undergo rapid homodimerization.
- Their homodimers can participate in CM as well as their monomer counterpart.
- Examples:
  - Terminal olefins
  - Primary allylic alcohols
  - Esters

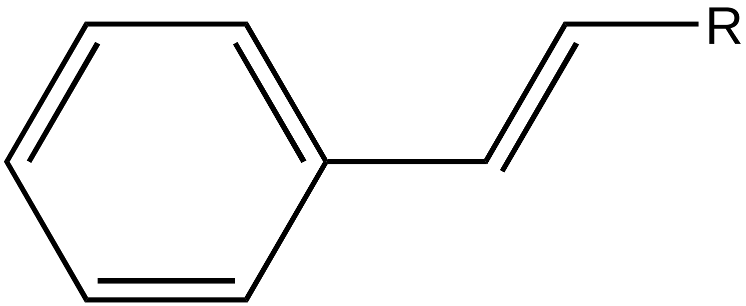


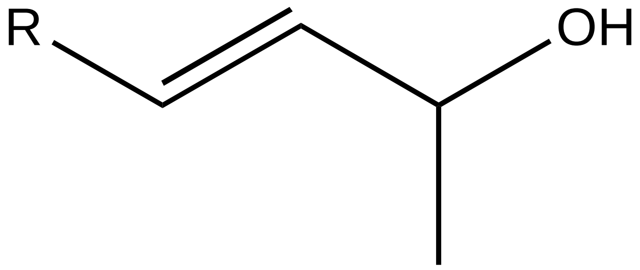




Type II - Slow homodimerization

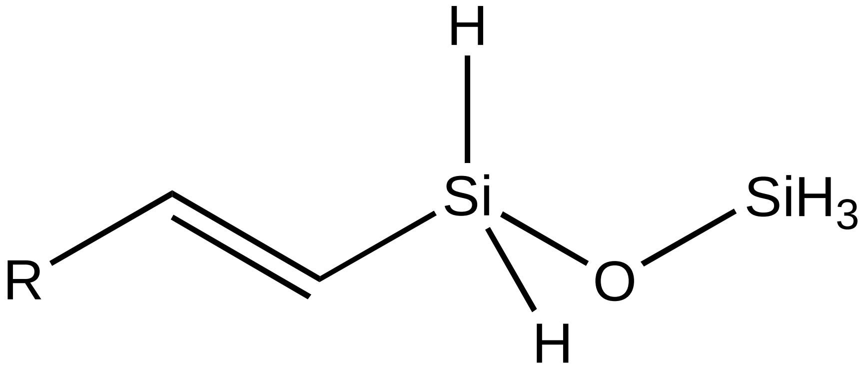
- Olefins that homodimerize slowly.
- Their homodimers can be only sparingly consumed in subsequent CM reactions.
- Examples:
  - Styrenes
  - Secondary allylic alcohols





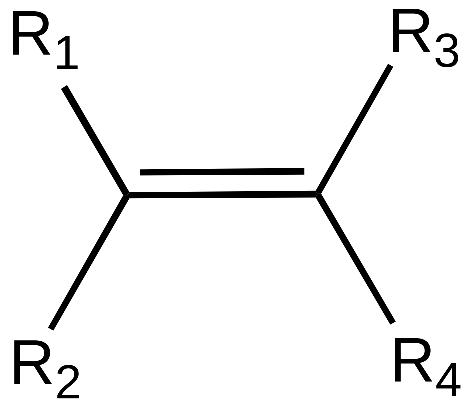
Type III - No homodimerization

- Olefins that are essentially unable to be homodimerized but can undergo CM with type I or II olefins.
- Examples:
  - Vinyl siloxanes



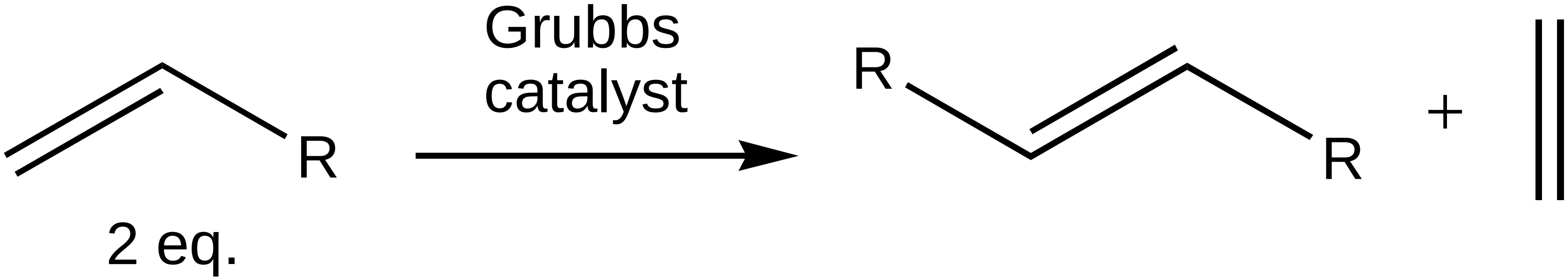
Type IV - Spectators

- Olefins that cannot participate in CM, but do not inhibit catalyst activity towards other olefins.
- Examples:
  - Quaternary allylic carbon-containing olefins



CM of Terminal Olefins

- CM reactions of terminal olefins produce ethene.
- Ethene can be easily removed from the mixture.
- This causes the forward reaction (and thus desired product) to be favoured.



Reactivity

- Reacting two olefins of the same type produces a non-selective (often statistical) mixture.
- Reacting two olefins of different types often produces a selective product.

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Nonselective CM

- When two type I olefins are used in CM reactions, the reactivities of the homodimers and cross products towards secondary metathesis events are high.
- The desired cross product equilibrates with the various homodimers through secondary metathesis to produce a statistical mixture.
- Non-selective mixtures are also produced when two non-type I olefins of the same type are mixed, but with lower yields because of the olefins’ reduced reactivity.

Selecting in nonselective CM

- A 90% yield can be obtained from the reaction of two olefins of the same type if one olefin is used in 10 equivalent excess.

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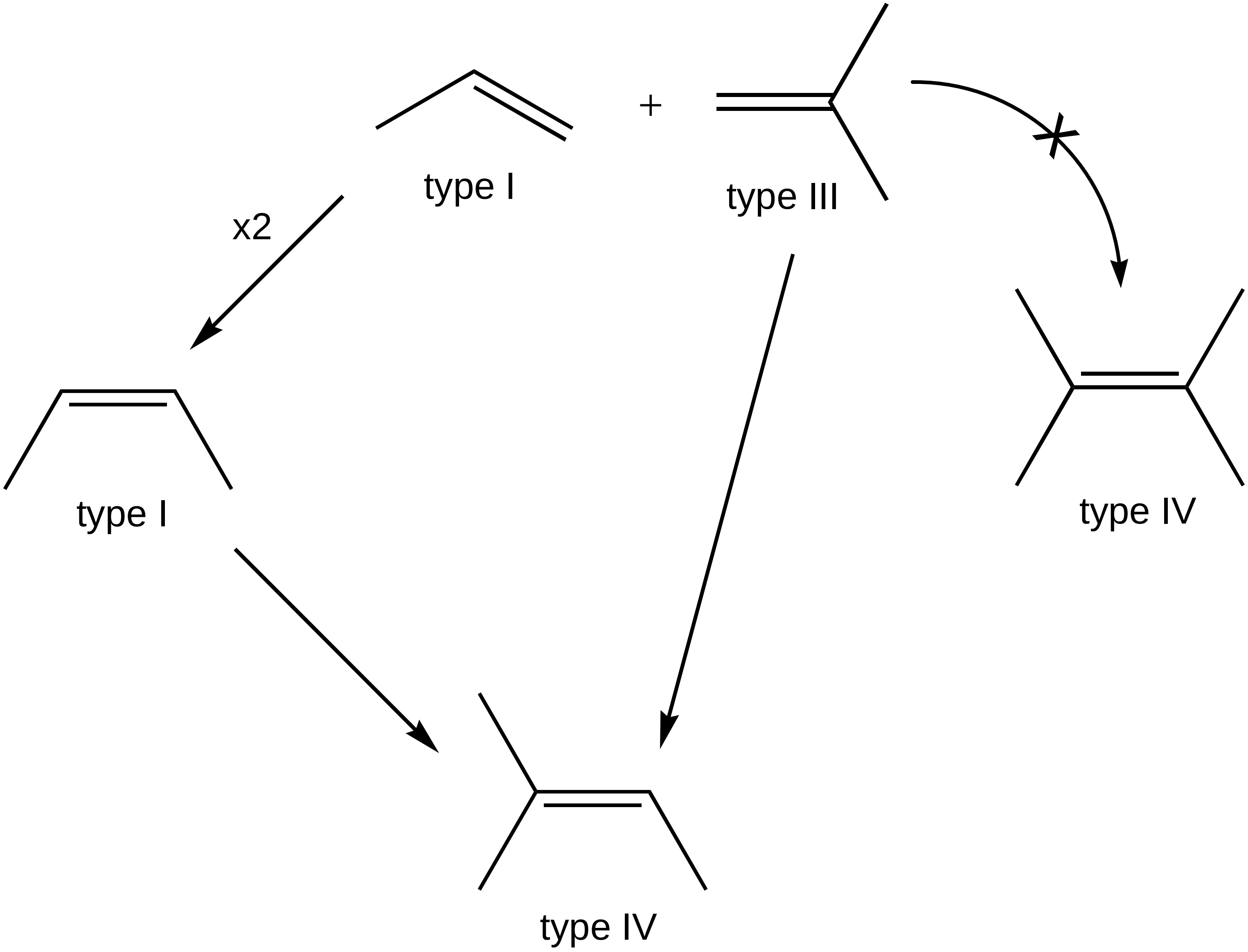
Selective CM

- The most effective selective CM reactions involve the reaction of a type I olefin with a less reactive type II or III olefin.
- The less reactive olefin undergoes homodimerization at a much slower rate (or not at all), so even if the type I olefin homodimerizes, the product distribution will be driven towards the desired cross product.
- The produced cross product will be relatively stable to the catalyst, so a statistical mixture will not be formed.

Selective CM



Type I and Type II Olefins

- This reaction commonly results in selective cross-metathesis reactions with high stereoselectivity.
- The Type II olefin will undergo a cross metathesis reaction with the Type I olefin.
  - The Type I olefin will form a homodimer which will then undergo a CM reaction with the Type II olefin.
- Interestingly, smaller protecting groups seem to favour the trans- product.

Type I and Type III Olefins

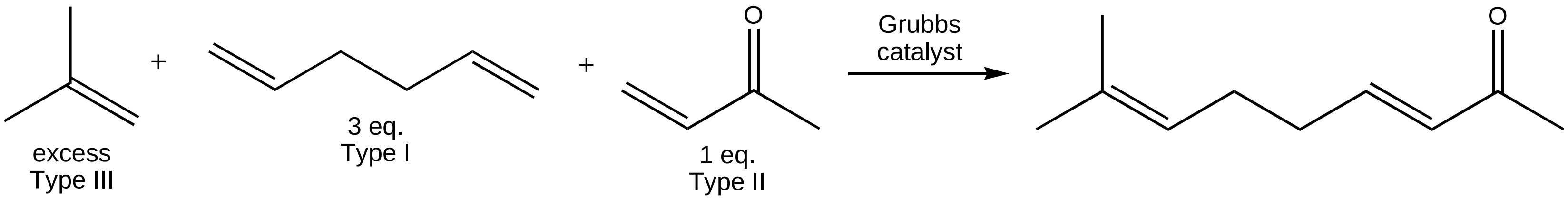
- Type III olefins commonly have a lot of steric bulk, so they will very rarely form the homodimer product.
- Among the first reactions that show exclusive trans- olefin selectivity.
  - Selectivity is based only on steric effects of alkyl substituents.
- Steric bulk also limits further tertiary metathesis from occurring with the product.
- The same type of chemistry applies to reactions between Type II and Type III olefins.

Bridge Type Olefins

- This term refers to reactants that can belong to more than one category of olefin.
- In general reactivity depends very strongly on substituent patterns and catalyst choice.
- Different catalysts will have different effects on the products obtained.

Three Component Reactions

- Challenging method to develop due to low selectivity of some processes.
- However it has been shown that the use of selective cross metathesis makes these reactions possible.
  - Selective metathesis can result in slow secondary metathesis.
  - Can use olefins that do not undergo a cross metathesis reaction allowing a third olefin (commonly a diene) to react with both olefins resulting in an asymmetrical product.

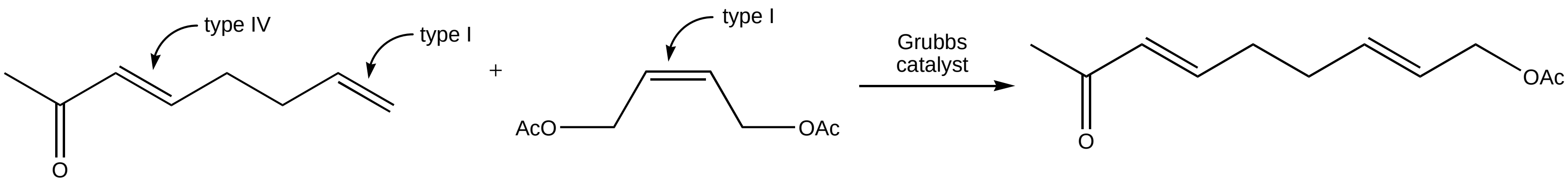


Three Component Reactions

- The reaction of the three olefins will dominantly yield one specific steroisomer.
  - Due to the reaction conditions mentioned above, such as adding an excess of the Type III olefin and 1 equivalent of the Type II olefin.
- Theoretically the combination of any Type I, Type II, and Type III olefin should yield a three component, asymmetrical product.
  - This leads to new complexity in olefin reactivity and new series of reactions to investigate.

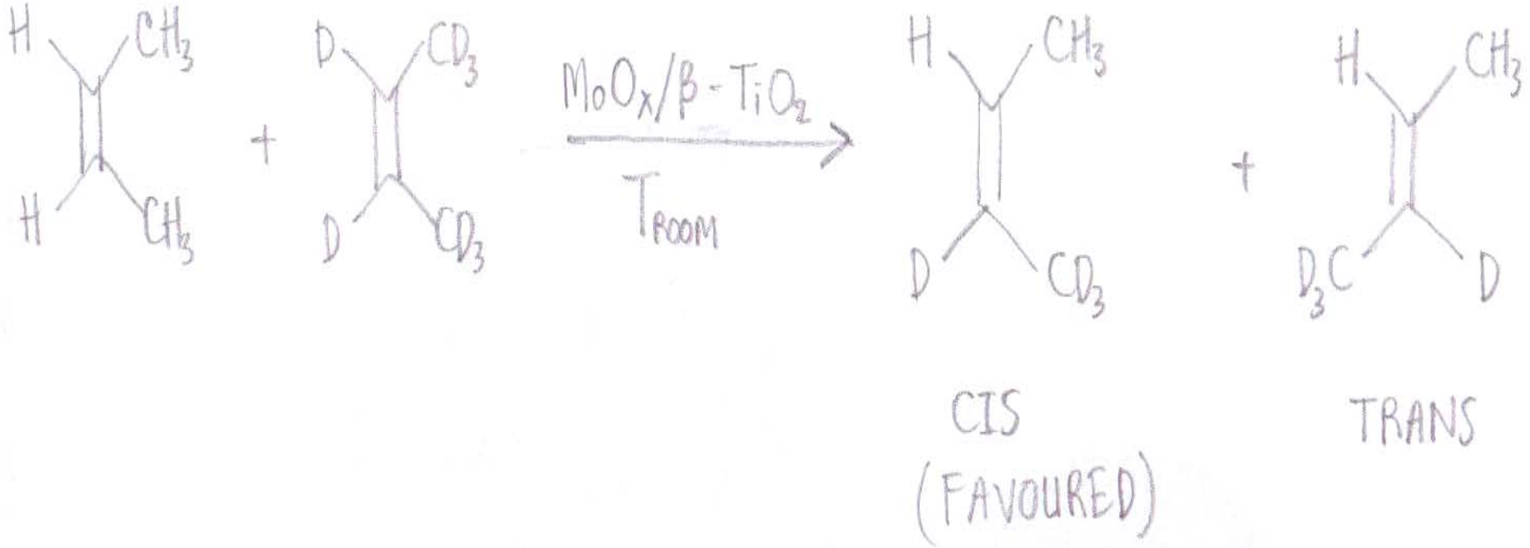
Regioselectivity & Chemoselectivity

- The type categorization allows for predictions in product selectivity, but can also be applied to the prediction of chemoselective reactions.
  - For example, reaction between a Type I or Type II olefin with Type VI allows for selective reactivity between the Type I dimer and another Type I olefin due to the fact that Type VI olefins are not reactive.

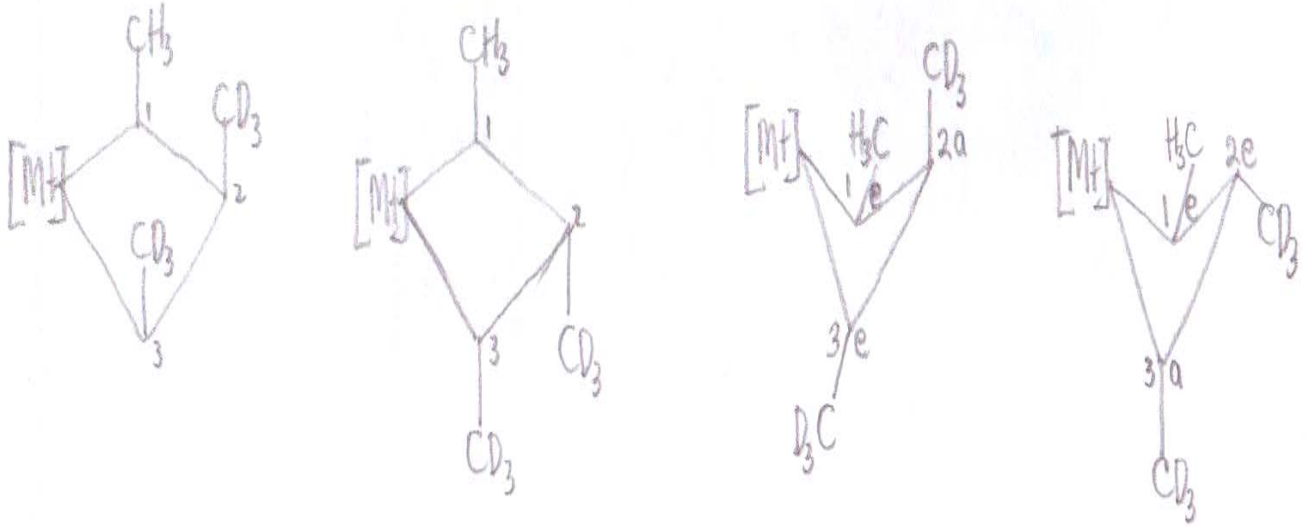


- Adding steric bulk will help in producing high olefin stereoselectivity because the product essential becomes non-reactive.

Stereochemistry



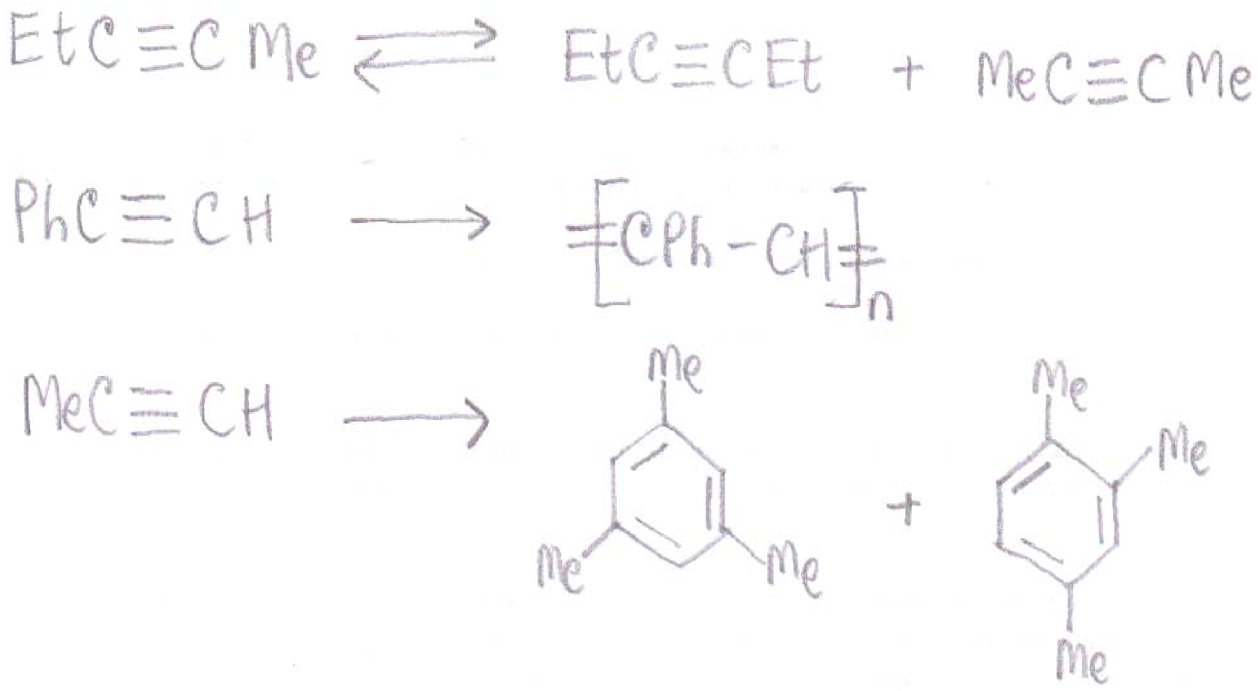
Stereochemistry: Intermediate



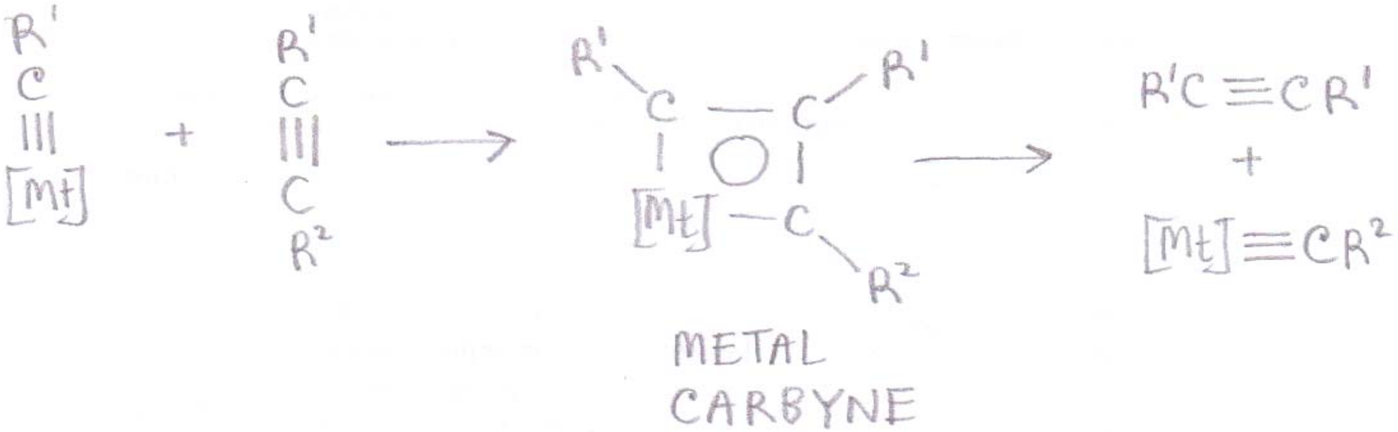
- seems “trans” favour
- Bent → axial and equitorial
- 1,3 dominant over 1,2
- bulkier substituent, 1,2 become more dominant
- 1,3→ee<ae<aa in energy
- 1,2→ee,aa<ea
- Molybdenum > Tungsten in stereoselectivity due to shorter [Mt]—C bond

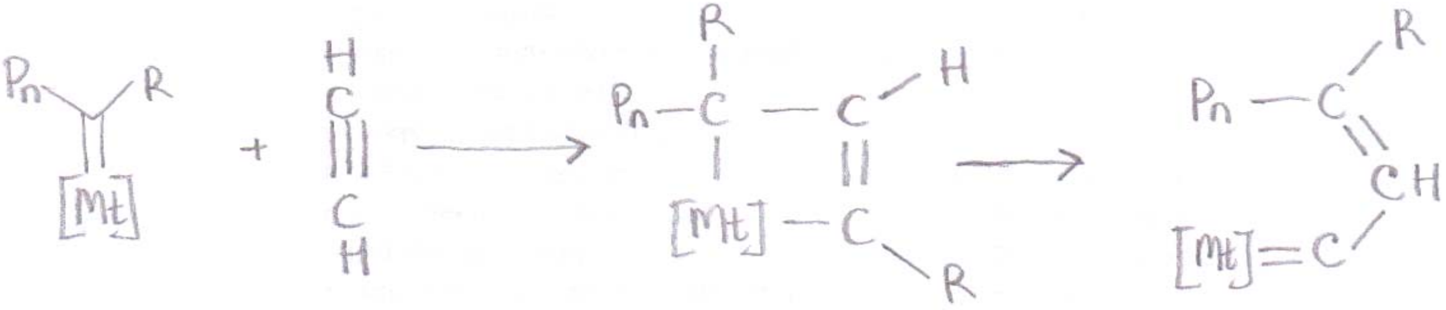
Alkyne metathesis

Alkyne Metathesis

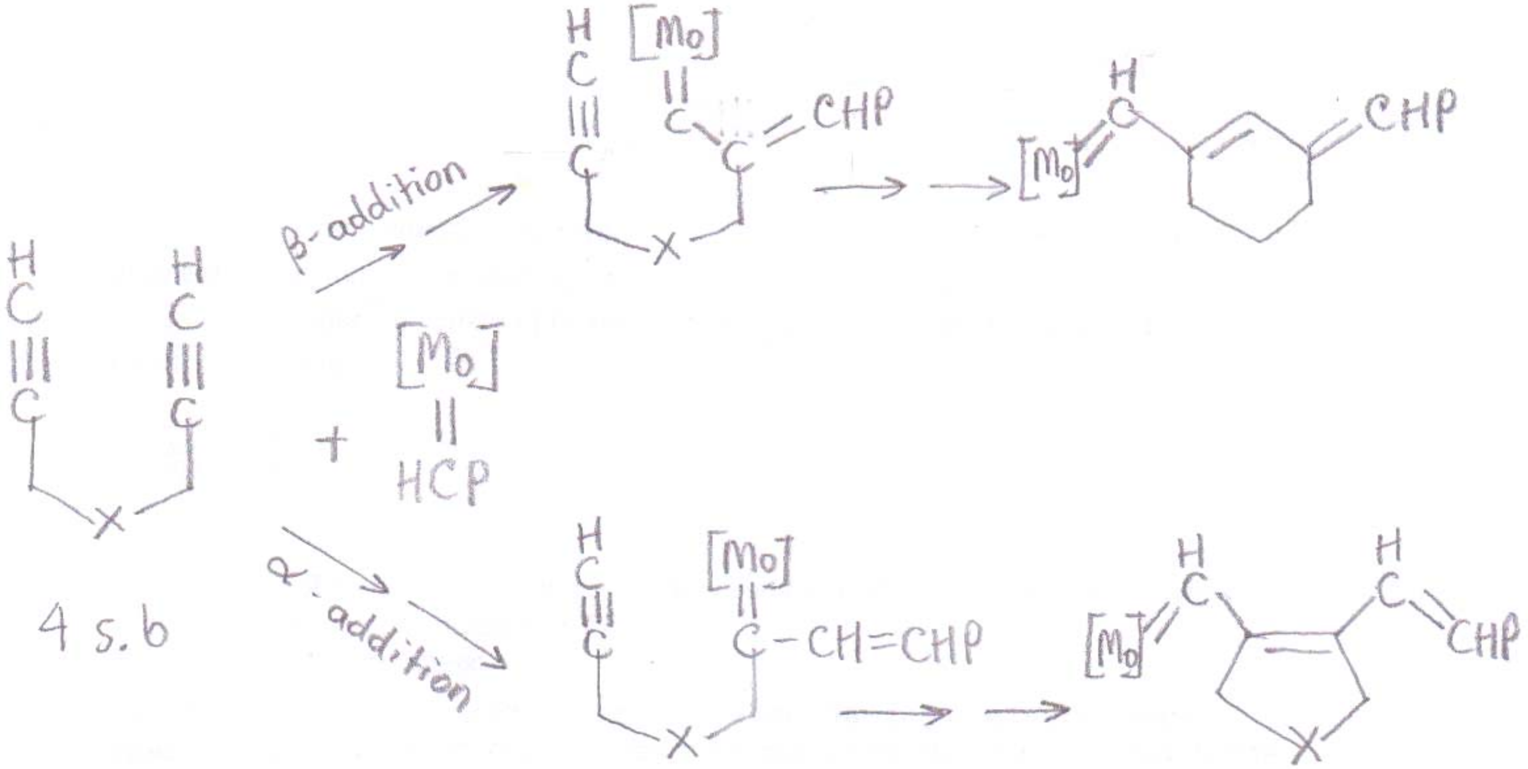


Alkyne Metathesis: Mechanism



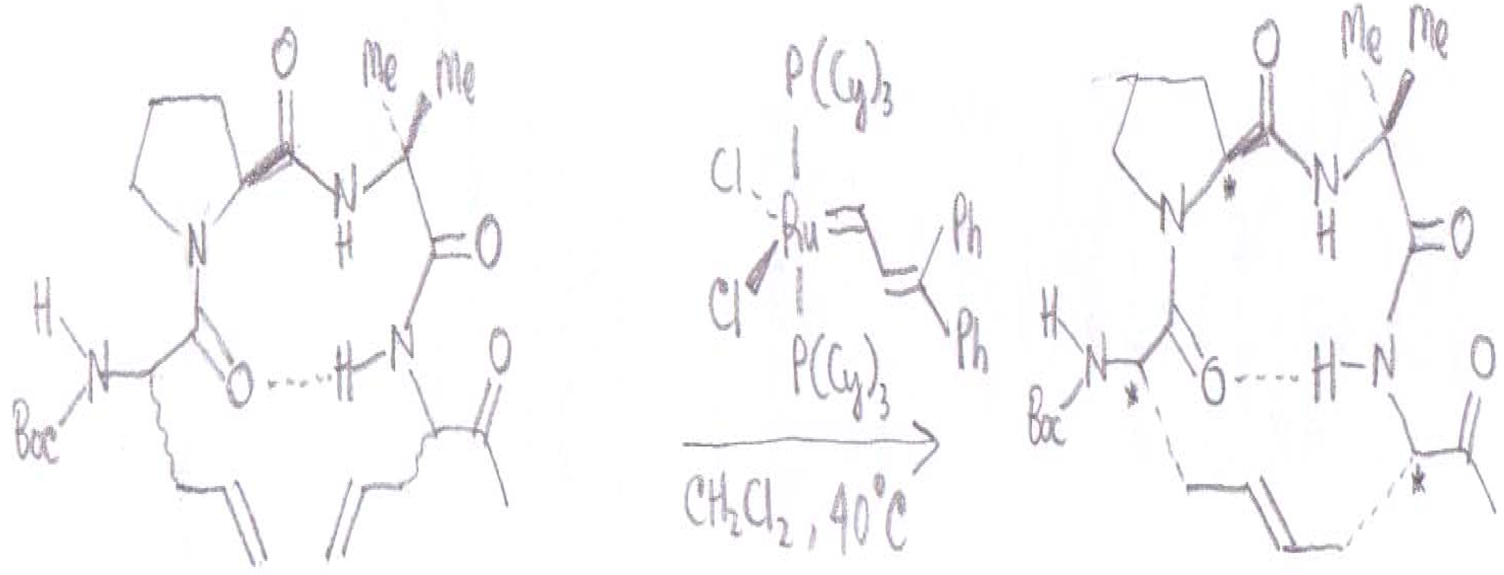


Diynes Metathesis



Examples

Dienes Metathesis: Application



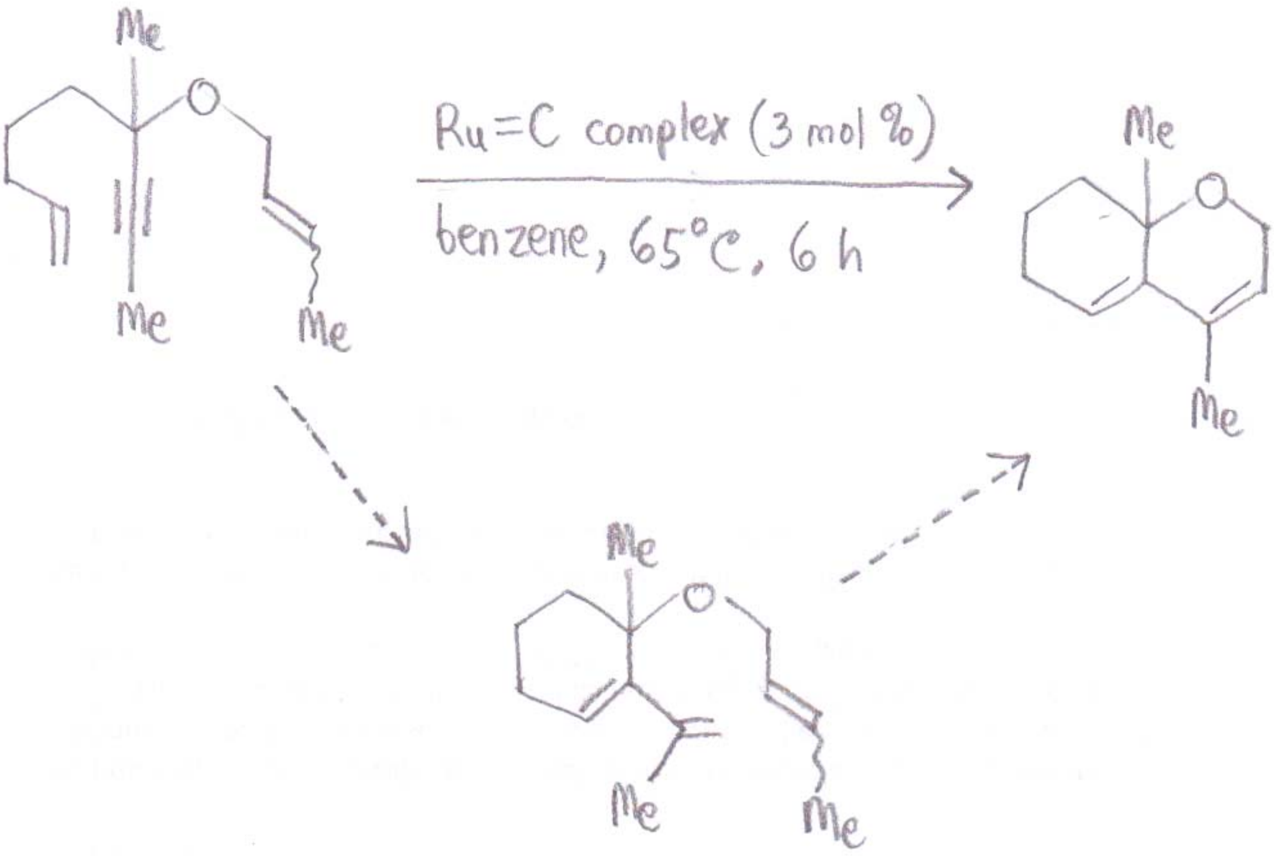
4 DIASTEREOMERS

14 ATOMS AWAY

1 PRODUCT

(S,S,S)

Alkyne Metathesis: Application



(+) passifloricin A

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Calystegine A$_7$

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Applications

Polymer cracks

- Structural polymers are susceptible to cracks.
- These cracks often form deep within the structure where detection is difficult and repair is almost impossible.
- Cracking can lead to anything from mechanical degradation of fibre-reinforced polymer composites to electrical failure (when the cracks occur in microelectronic polymeric components).

Autonomic healing

- An efficient method of repairing these cracks is autonomic healing.
- In autonomic healing, microencapsulated healing agent and catalytic chemical trigger are incorporated into the polymer within an epoxy matrix.
- When a crack is formed, it ruptures embedded microcapsules, which releases healing agent into the crack plane through capillary action.
- Polymerization of the healing agent is then triggered by contact with the embedded catalyst to bond the crack faces.

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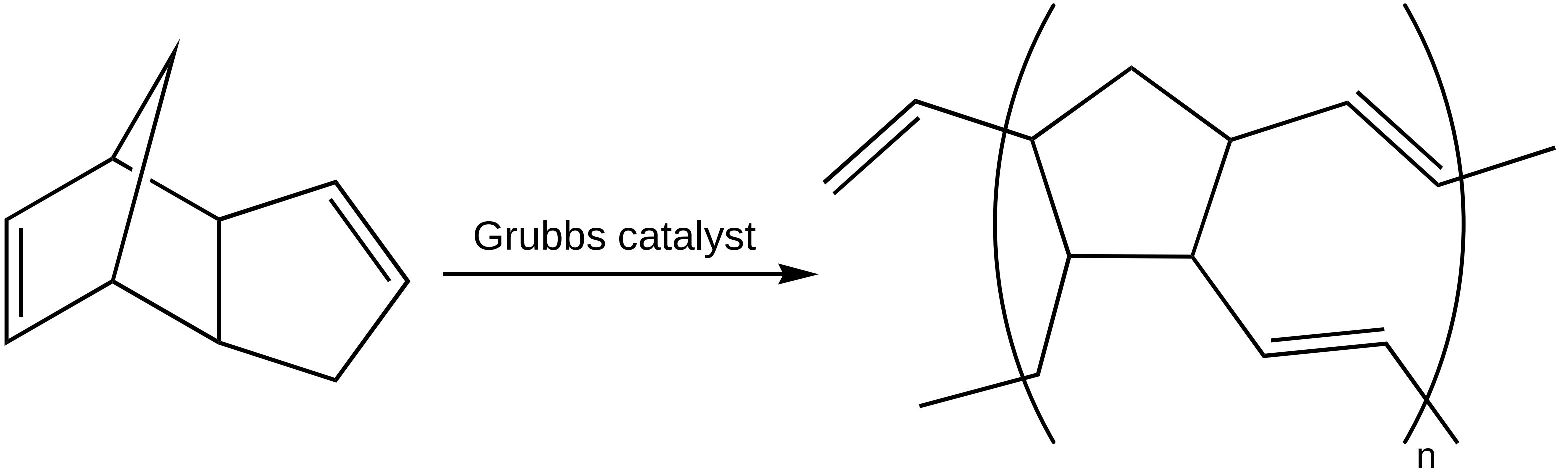
Autonomic healing with Grubbs

- The reaction used in trials of autonomic healing was metathesis of dicyclopentadiene with a Grubbs catalyst.



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Questions?