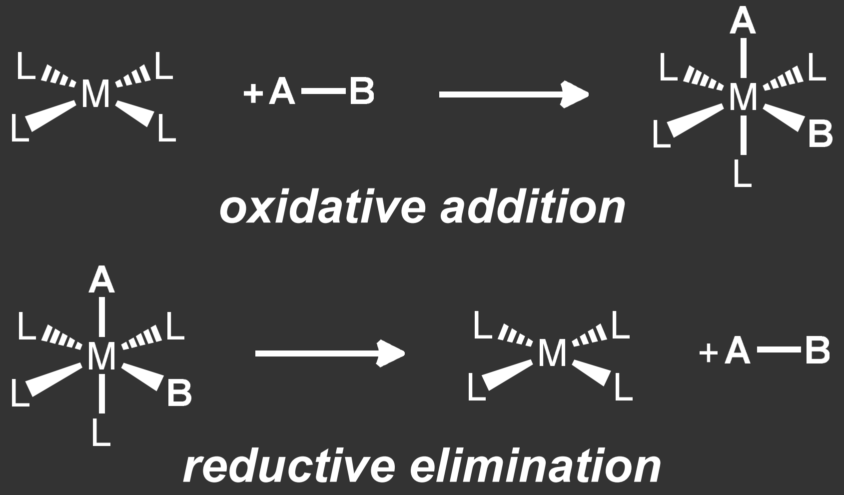
Losing and Gaining Electrons

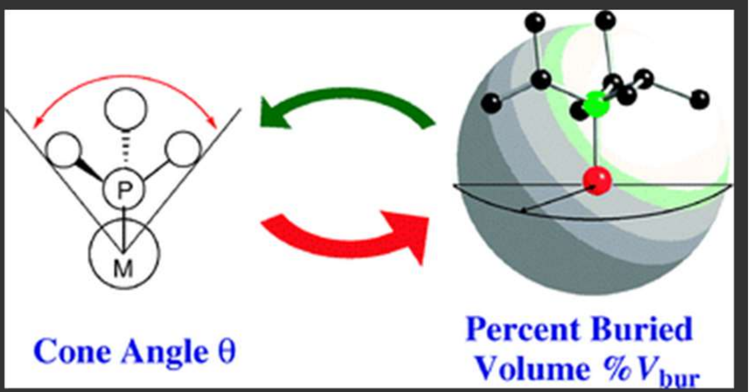
If we consider association and dissociation as the full reaction, we can sub-divide this concept into four basic reactions:

Type	Coord. Number	Oxidation State
Addition (Association)	Increase	Same
Elimination (Dissociation)	Decrease	Same
Oxidative Addition	Increase	Increase
Reductive Elimination	Decrease	Decrease



Percent Buried Volume, %V_{bur}

The strength of the metal-ligand bond is often judged by the bond length, M-L.



This is affected by the force constant of the bond (“k”) and the steric hindrance of the ligand.

The steric hindrance of the ligand is judged by the “cone angle” (i.e., the solid angle) that the ligand occupies around the imaginary first coordination sphere.

Both of these factors can be incorporated into the concept of the “% buried volume”, the volume of the ligand inside the coordination sphere.

Image liberated from: H. Clavier and S. P. Nolan, Chem. Commun., ***2010****, 46, 841-861.*

Steric Bulk vs. Bond Strength

This concept is valuable because it incorporates both electronic (bond length) and steric (cone angle) factors. However, “estimating” the volume is tricky.

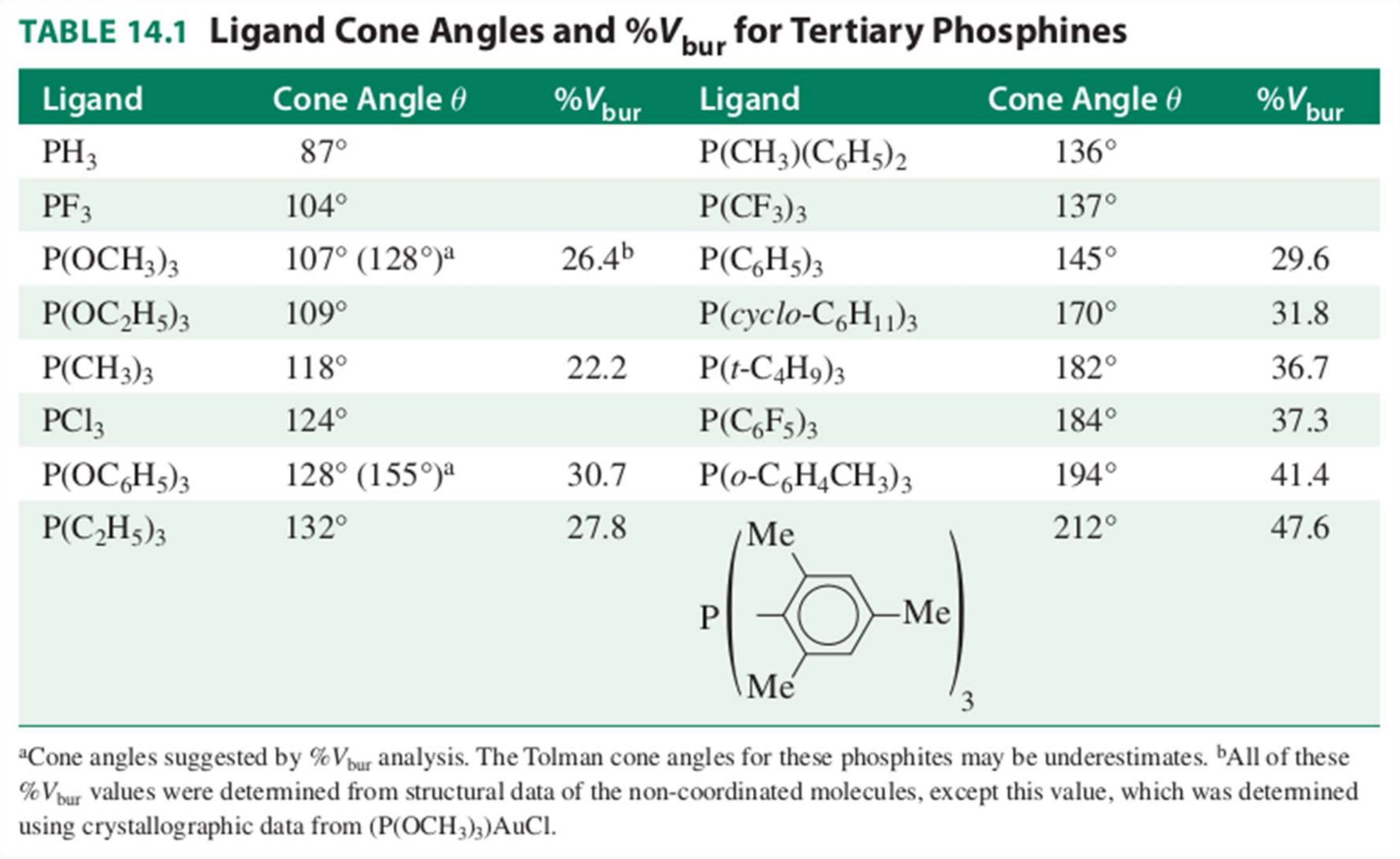


TABLE 14.1 Ligand Cone Angles and %V_{bur} for Tertiary Phosphines

Ligand	Cone Angle θ	%V_{bur}	Ligand	Cone Angle θ	%V_{bur}
PH_3	87°		$P(CH_3)(C_6H_5)_2$	136°	
PF_3	104°		$P(CF_3)_3$	137°	
$P(OCH_3)_3$	107° (128°)[a]	26.4[b]	$P(C_6H_5)_3$	145°	29.6
$P(OC_2H_5)_3$	109°		$P(\mathit{cyclo}\text{-}C_6H_{11})_3$	170°	31.8
$P(CH_3)_3$	118°	22.2	$P(t\text{-}C_4H_9)_3$	182°	36.7
PCl_3	124°		$P(C_6F_5)_3$	184°	37.3
$P(OC_6H_5)_3$	128° (155°)[a]	30.7	$P(o\text{-}C_6H_4CH_3)_3$	194°	41.4
$P(C_2H_5)_3$	132°	27.8		212°	47.6

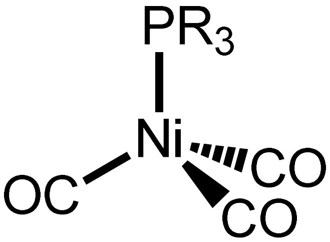
[a] Cone angles suggested by %V_{bur} analysis. The Tolman cone angles for these phosphites may be underestimates. [b] All of these %V_{bur} values were determined from structural data of the non-coordinated molecules, except this value, which was determined using crystallographic data from $(P(OCH_3)_3)AuCl$.

Tolman Electronic Parameter

The “Tolman Electronic Parameter” (TEP) is the decrease in the IR signal of a carbonyl ligand from “free” carbonyl (2143 cm^{-1}) when in a compound with a phosphine.

These are typically judged from the tetrahedral nickel compounds Ni(PR$_3$)(CO)$_3$. The stretch used is the “A$_1$” fully symmetrical stretch of the CO compound.

This idea is used commonly in discussing the steric effect of a ligand.

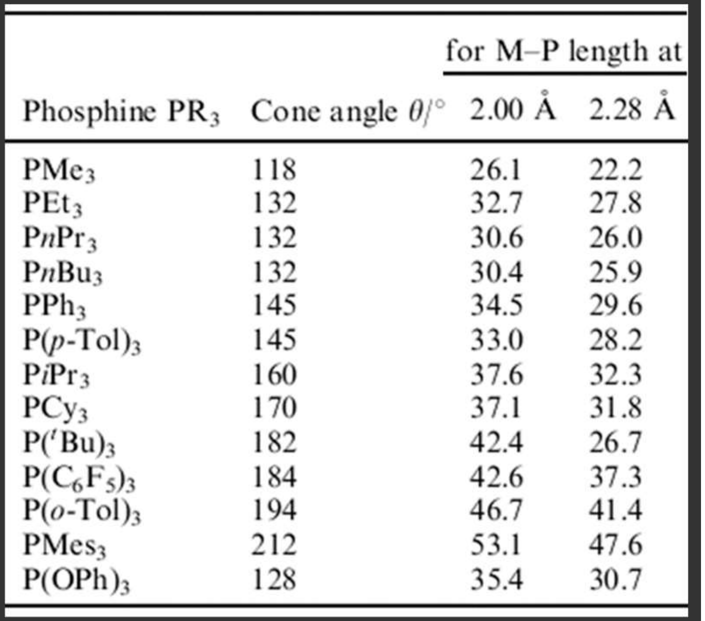


L	***v(CO) cm^{-1}***
P(t-Bu)$_3$	2056.1
PMe$_3$	2064.1
PPh$_3$	2068.9
P(OEt)$_3$	2076.3
PCl$_3$	2097
PF$_3$	2110.8

Steric Bulk

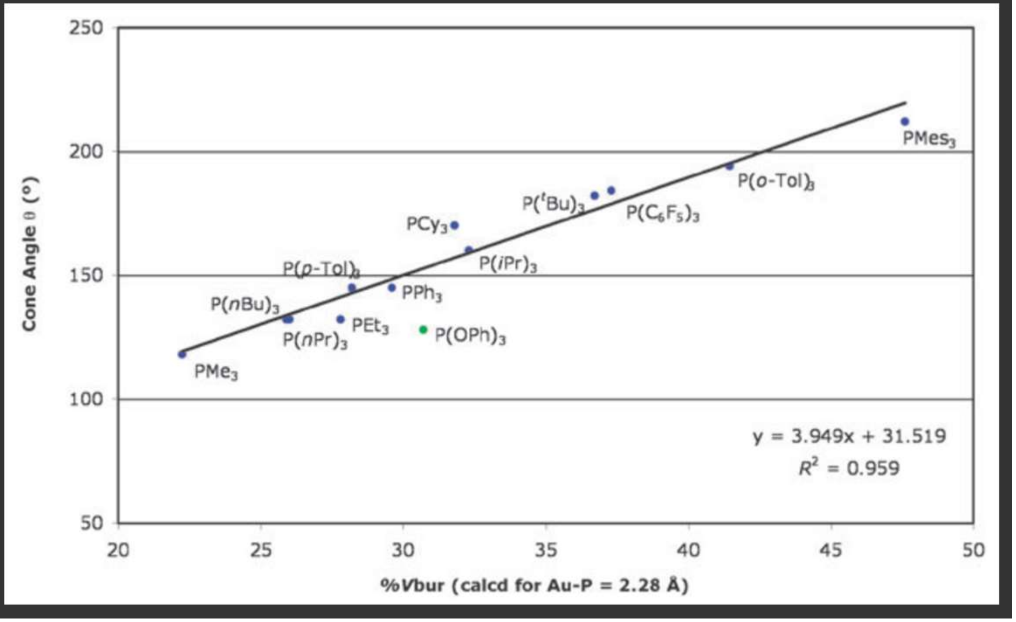
Cone angle, %V_{bur}, and TEP can all be related. Generally, the method is to set a “standard” M-P bond length and coordination sphere radius.

The TEP or cone angle can then give you a conceptual %V_{bur} to compare a variety of ligands for their steric bulk.



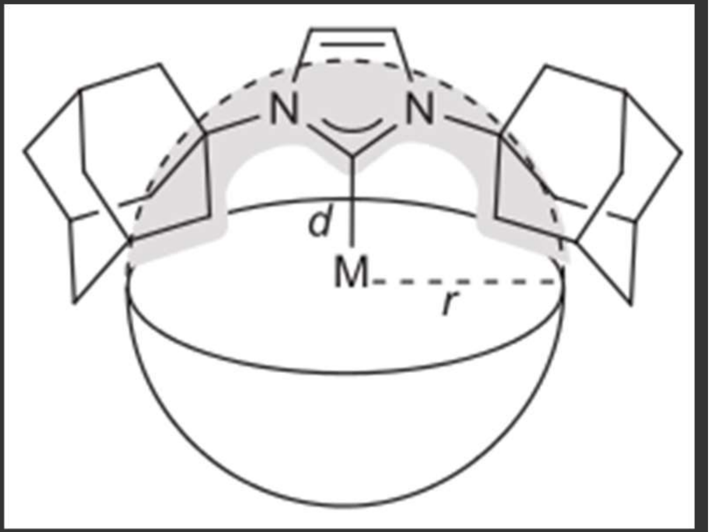
Phosphine PR_3	Cone angle θ/°	for M–P length at 2.00 Å	for M–P length at 2.28 Å
PMe_3	118	26.1	22.2
PEt_3	132	32.7	27.8
$P\textit{n}Pr_3$	132	30.6	26.0
$P\textit{n}Bu_3$	132	30.4	25.9
PPh_3	145	34.5	29.6
$P(\textit{p}\text{-}Tol)_3$	145	33.0	28.2
$P\textit{i}Pr_3$	160	37.6	32.3
PCy_3	170	37.1	31.8
$P(^tBu)_3$	182	42.4	26.7
$P(C_6F_5)_3$	184	42.6	37.3
$P(\textit{o}\text{-}Tol)_3$	194	46.7	41.4
$PMes_3$	212	53.1	47.6
$P(OPh)_3$	128	35.4	30.7

Steric bulk is a way to change the reactivity of a metal centre.



H. Clavier and S. P. Nolan
Chem. Commun., ***2010***, *46, 841-861.*

TEP and %V_{bur} for Carbenes



The %V_{bur} values, however, may vary greatly depending on the system used and care must be taken to compare only values determined using the same approach.

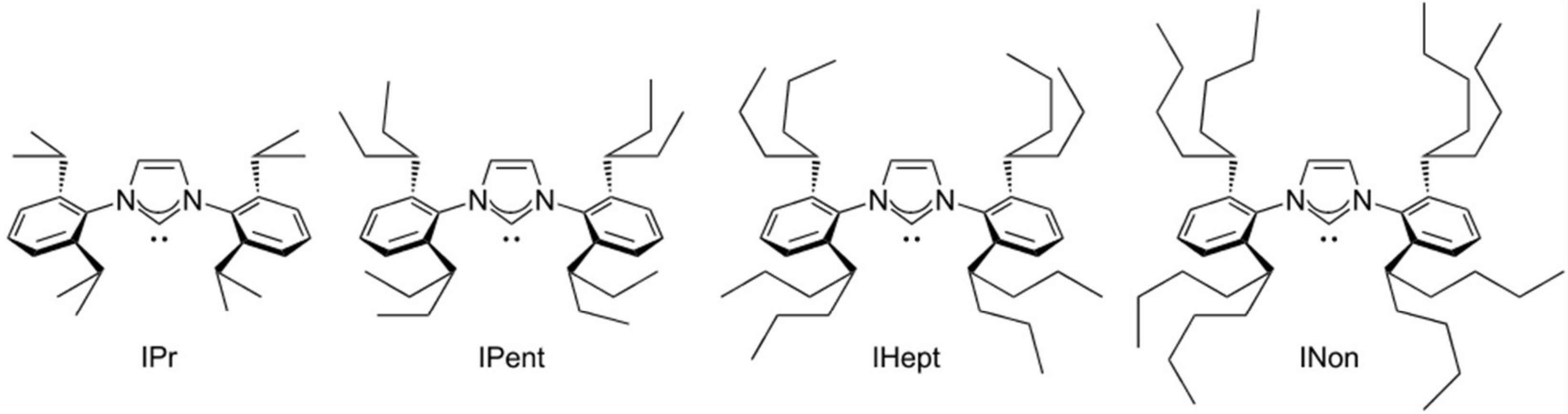
Fixed parameters:

- 2 Å for metal–carbene bond
- 3 Å or 3.5 Å for the sphere radius

A larger %V_{bur} value signifies a greater steric influence of the ligand on the metal centre

TEP and %V_{bur} for Carbenes

TEP specifically evaluates the electron-donating ability of a ligand by measuring the infrared-stretching frequencies of carbonyl ligands in model transition metal carbonyl complexes.

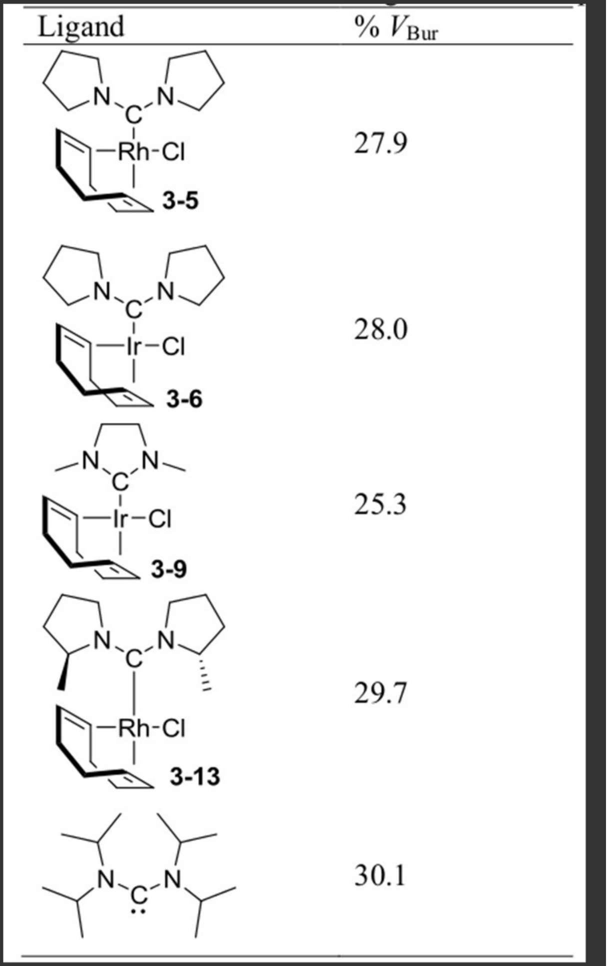


	IPr	IPent	IHept	INon
% V_{bur}	44.5%	I) 49.0% II) 48.6%	51.5%	51.3%
TEP_{DCM}	2051.5 cm^{-1}	2049.3 cm^{-1}	2048.6 cm^{-1}	2048.5 cm^{-1}
TEP_{hex}	2055.1 cm^{-1}	2053.1 cm^{-1}	2052.5 cm^{-1}	2052.1 cm^{-1}

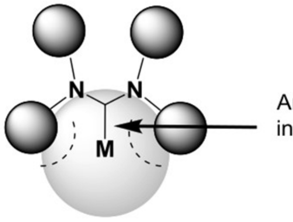
ADC vs. NHC

An “ADC” is an acyclic diaminocarbene. Given that the diference between an NHC and an ADC is the C-C bond in the backbone, one might expect ADCs to have a greater buried volume.

It turns out that these ligands are very similar to NHCs in their steric bulk.



Ligand	% V_{Bur}
3-5	27.9
3-6	28.0
3-9	25.3
3-13	29.7
	30.1

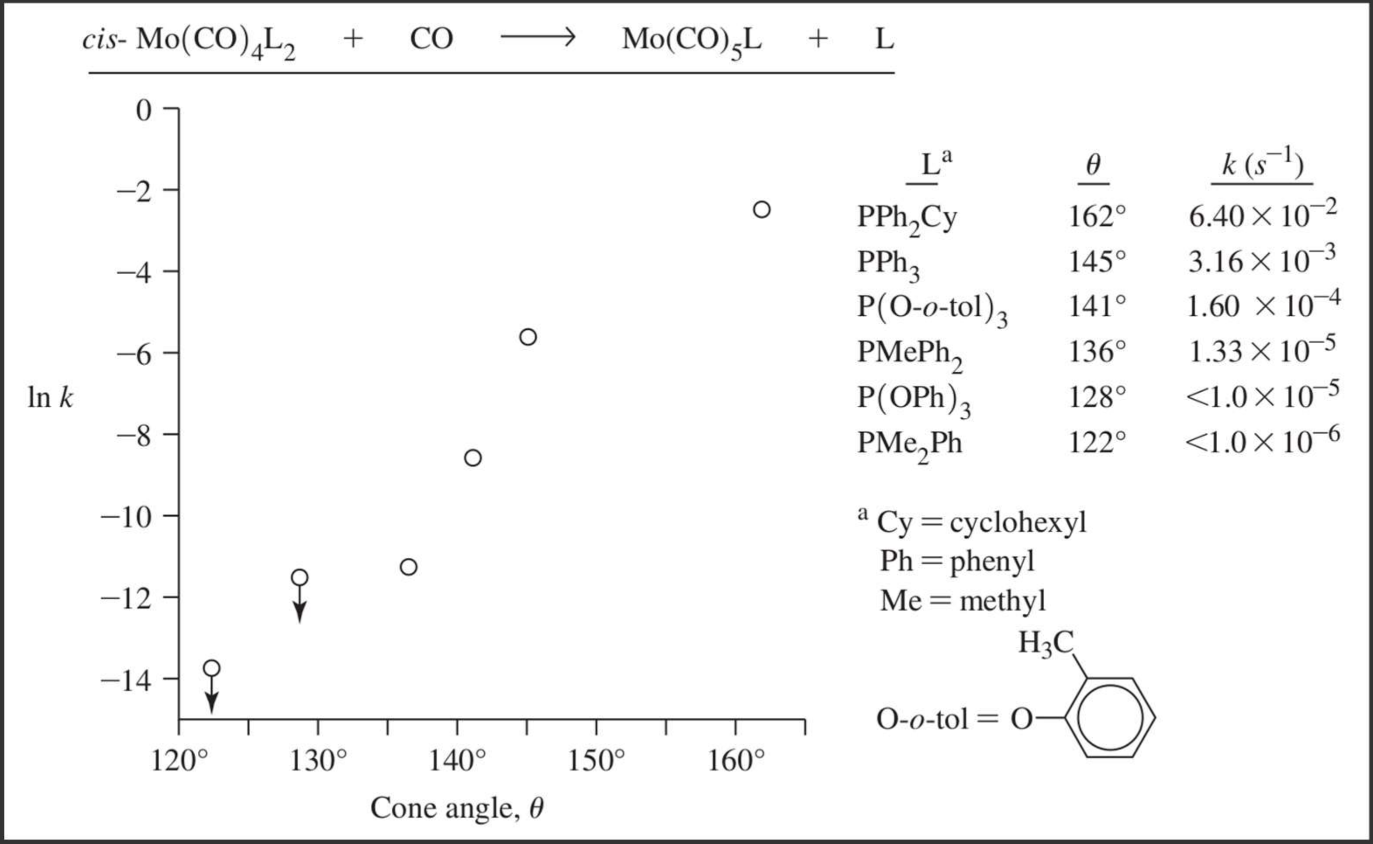


Amount of Ligand Intruding into Radius of Coordination Sphere is % V_{Bur}

D. R. Snead, PhD Thesis, U. of Florida, **2010**.

Sterics Can Predict Reactivity

The cone angle (or $\%V_{bur}$, or TEP) can predict kinetics, showing that steric bulk affects the rate of reactions. Note that the system has to be free of other influences that might complicate observing this trend.



$$cis\text{-}\ Mo(CO)_4L_2 + CO \longrightarrow Mo(CO)_5L + L$$

L^a	θ	$k\ (s^{-1})$
PPh_2Cy	162°	6.40×10^{-2}
PPh_3	145°	3.16×10^{-3}
$P(O\text{-}o\text{-}tol)_3$	141°	1.60×10^{-4}
$PMePh_2$	136°	1.33×10^{-5}
$P(OPh)_3$	128°	$<1.0 \times 10^{-5}$
PMe_2Ph	122°	$<1.0 \times 10^{-6}$

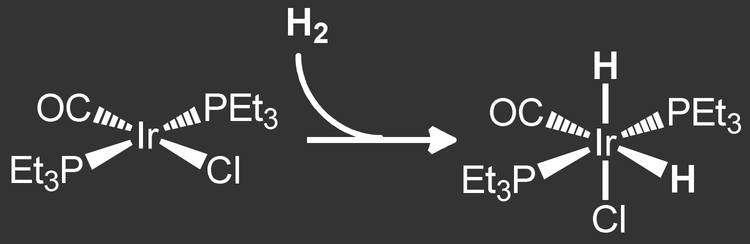
[a] Cy = cyclohexyl
Ph = phenyl
Me = methyl

Oxidative Addition

Oxidative addition increases everything by two:

- Coordination number
- Metal formal charge
- Electron count

So, square planar, 16 e$^-$ compounds can become 18 e$^-$ octahedral complexes by oxidative addition:



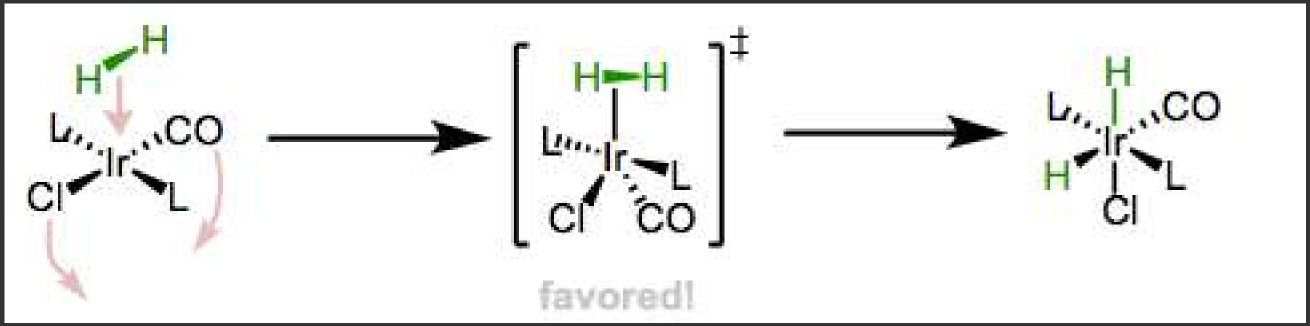
sqpl
d^8, *16* e$^-$
Ir^{+1}

O_h
d^6, *18* e$^-$
Ir^{+3}

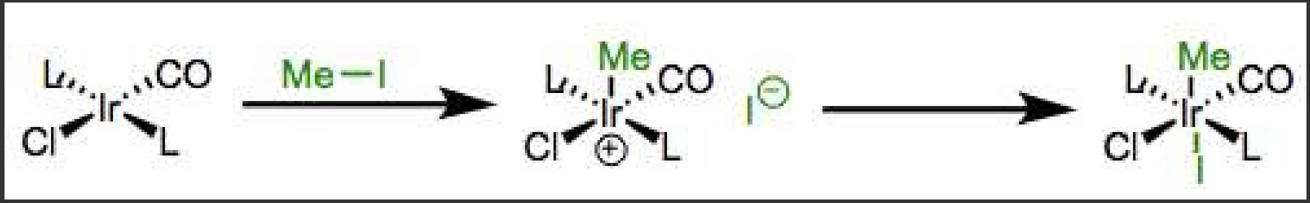
If this is a one-step addition, the groups add *cis*, if it is multiple step, it can be either *cis* or *trans.*

Mechanism

For non-polar bonds, the mechanism goes through a accociative step, with the transition state being coordination in an η^2 fashion to the bond. This will always be *cis*:

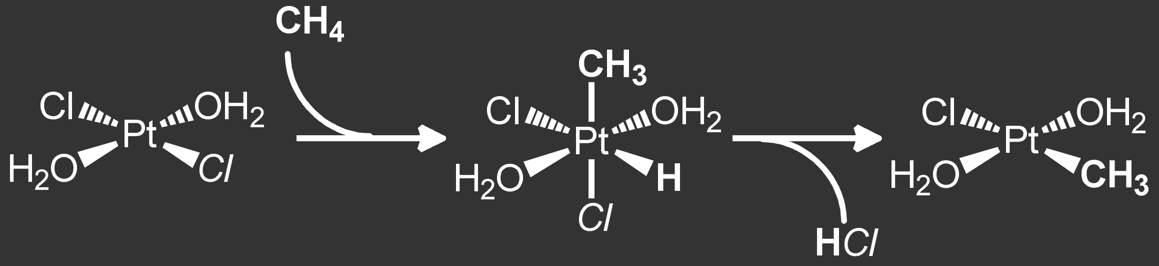


For polar bonds, the two different species are added step-wise, in an associative manner. This can be *cis* or *trans*:

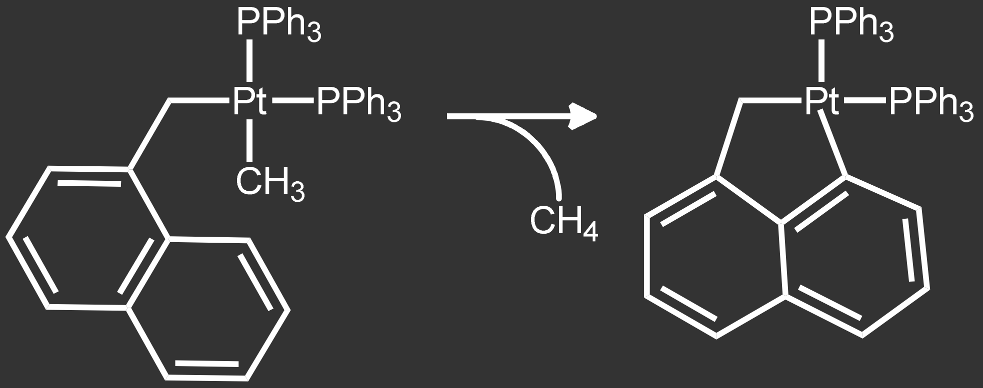


C-H Bond Activation

If the metal centre can access a C-H bond, it can add “into” this bond by oxidative addition:

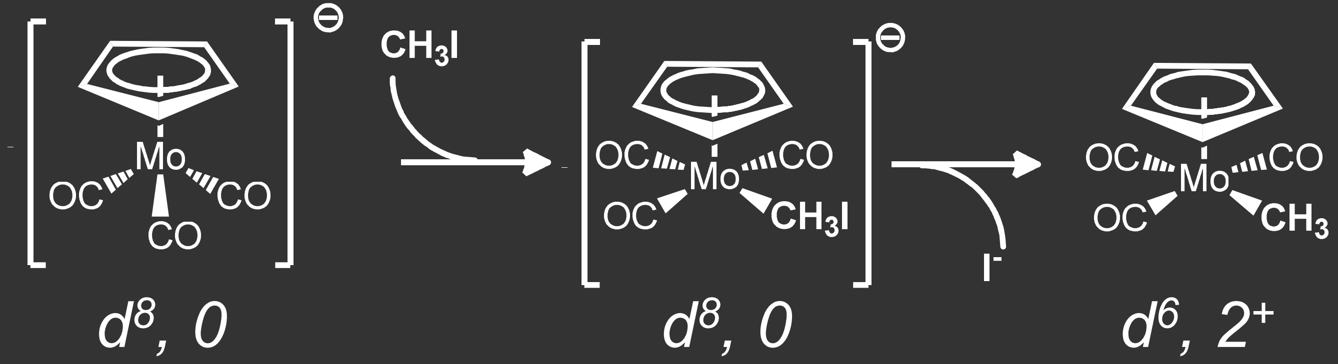


This oxidative addition can even occur in a ligand, creating a “metallocycle” (through “cyclometalation”):



Nucleophilic Displacement

Nucleophilic displacement has the same oxidation state changes as oxidative addition, but does not go through the double coordination:

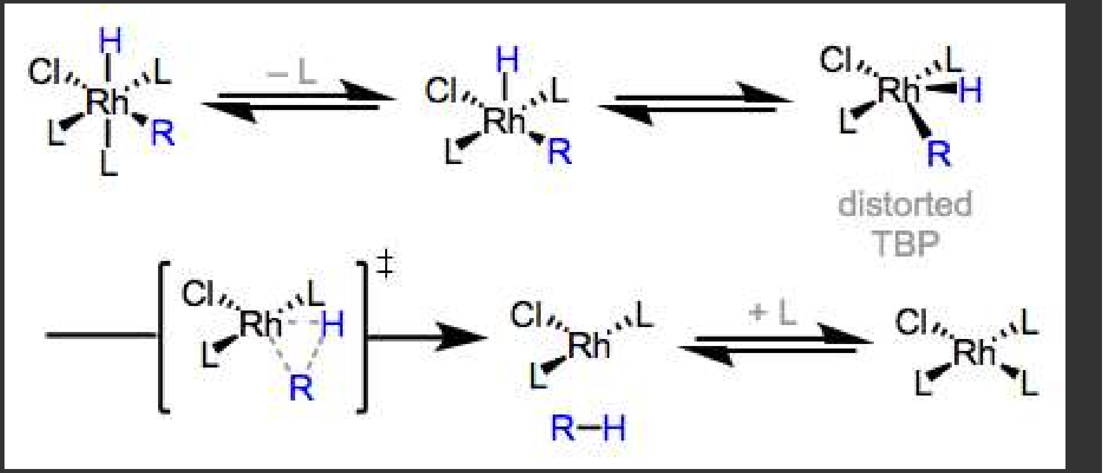


Rather, the ligand undergoes oxidation, and “passes it on” to the metal.

Reductive Elimination

Reductive elimination is the “opposite” of oxidative addition, and is the foundation of metal-mediated coupling reactions.

Typically it goes through a dissociation reaction, Berry pseudo-rotation, and then reductive elimination.

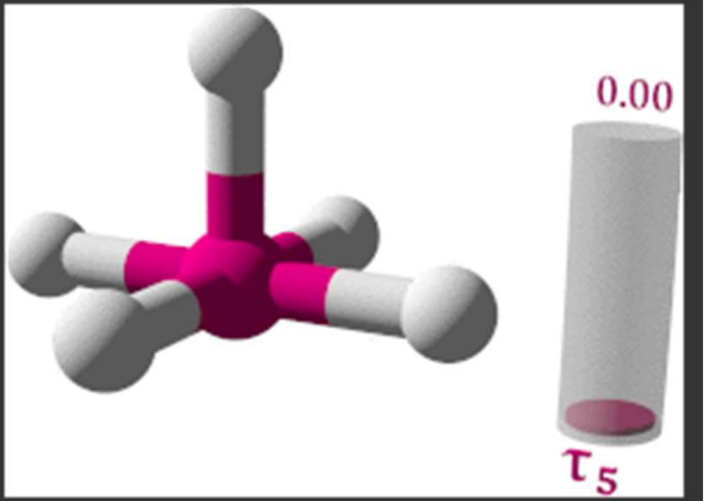


Like most dissociation reactions, the first step is typically rate-limiting.

$$(\eta^5\text{-}C_5H_5)_2TaH + H_2 \leftrightarrow (\eta^5\text{-}C_5H_5)_2TaH_3$$

$16\ e^-$	$18\ e^-$
+3	+5

Tau Parameter: TBP vs. Sqpy



I mentioned earlier that trigonal bipyramids are distinguished from square pyramids by the “tau” parameter (τ). This is calculated by the largest angle (β) and the second-largest angle (α):

$$\tau = \frac{\beta - \alpha}{60}$$

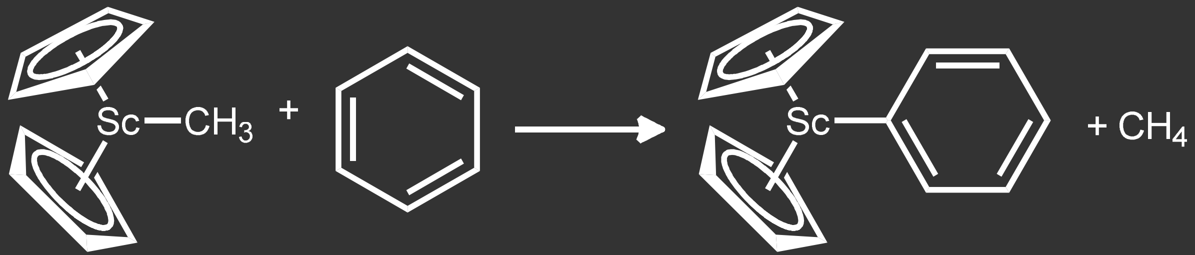
A symmetrical trigonal bipyramid has τ = 1, and a symmetrical square pyramid has τ = 0. Anything in between is “distorted.

Sigma Bond Metathesis

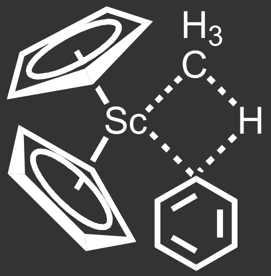
Metathesis (“switching”) is a key element in many reactions. For example, consider switching the C-H bond below:

$$CH_3^- + C_6H_6 \rightarrow CH_4 + C_6H_5^-$$

Although this is thermodynamically favourable (CH4 pKa = 49, C_6H_6 pK_a = 43), the idea of doing this is problematic. However, using an organometallic compound to mediate it makes it straightforward:



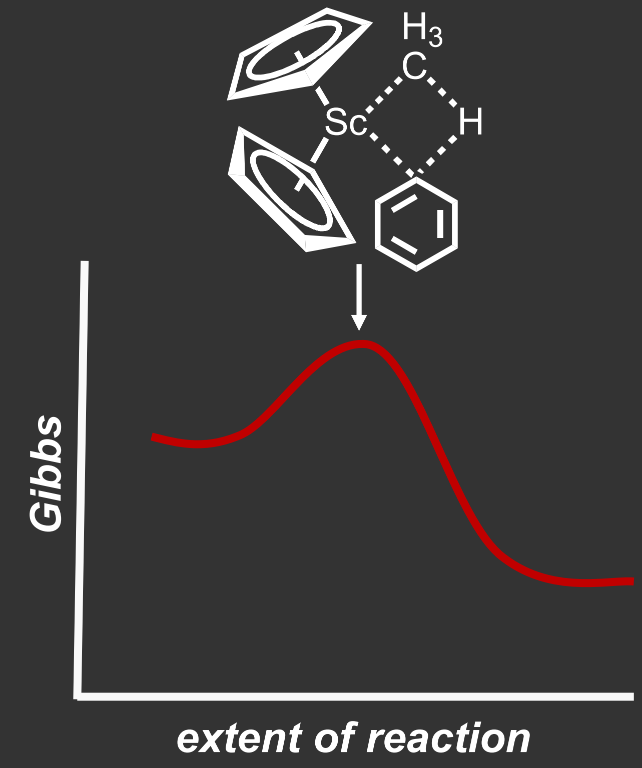
This appears to be simply oxidative addition followed by reductive elimination, but it is possible for it to occur in one step through a 4-centred transition state.

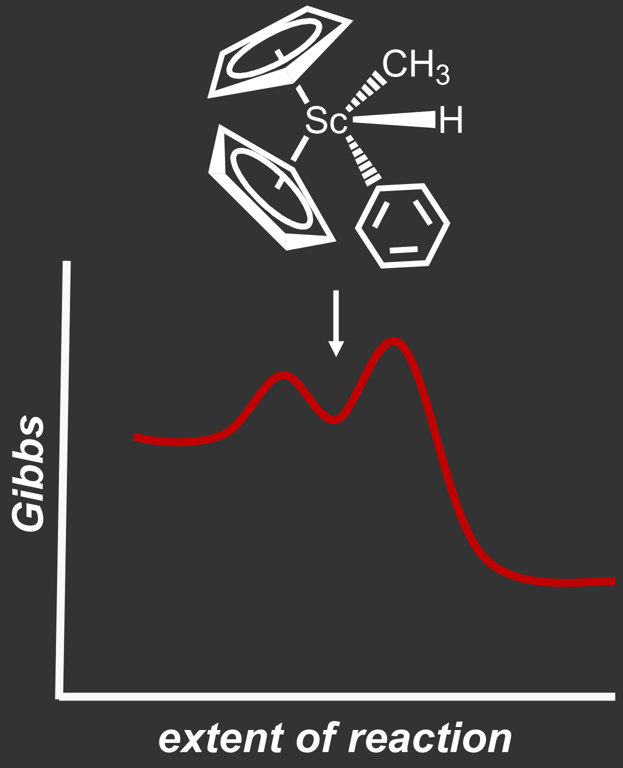


What Would the Difference Be?

Sigma bond metathesis is like a “concerted” oxidative addition and reductive elimination (they happen at the same time.

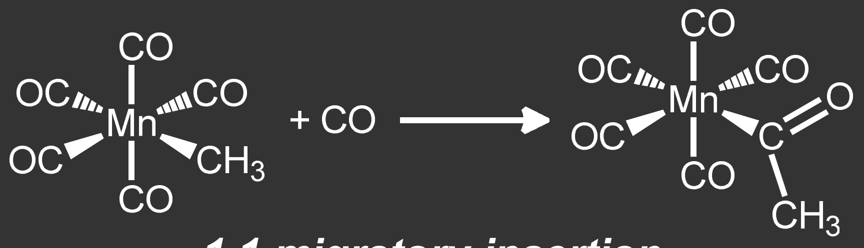
One could determine the difference by the lack of a higher oxidation state intermediate.





Insertion Reactions

Insertion reactions allow the modification of an existing ligand with a second. The new ligand stays formed at the metal centre, but can be removed as a new chemical compound:



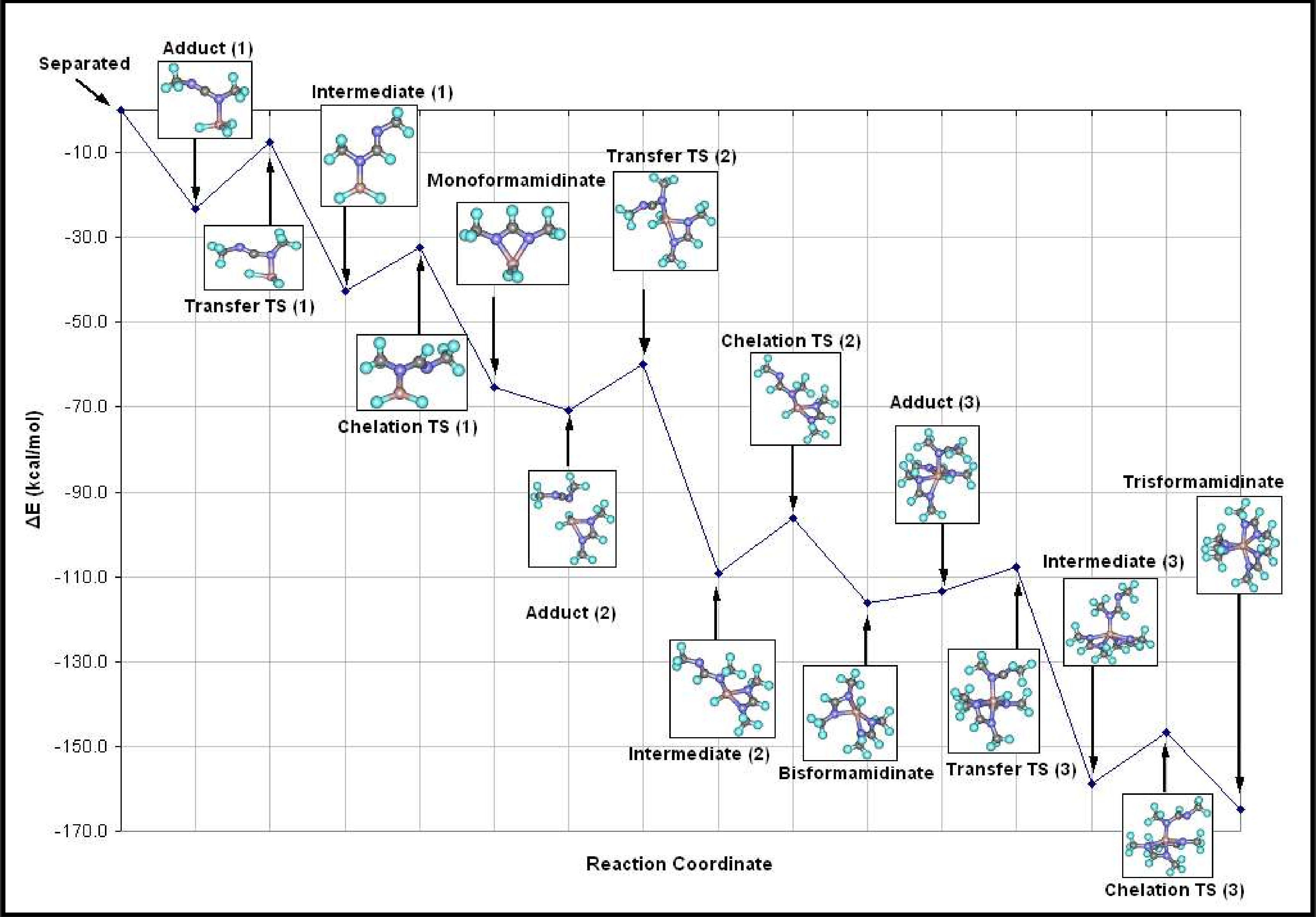
1,1 migratory insertion

There's obviously more than one step to this. The most typical is called a migratory insertion, and can be further differentiated:

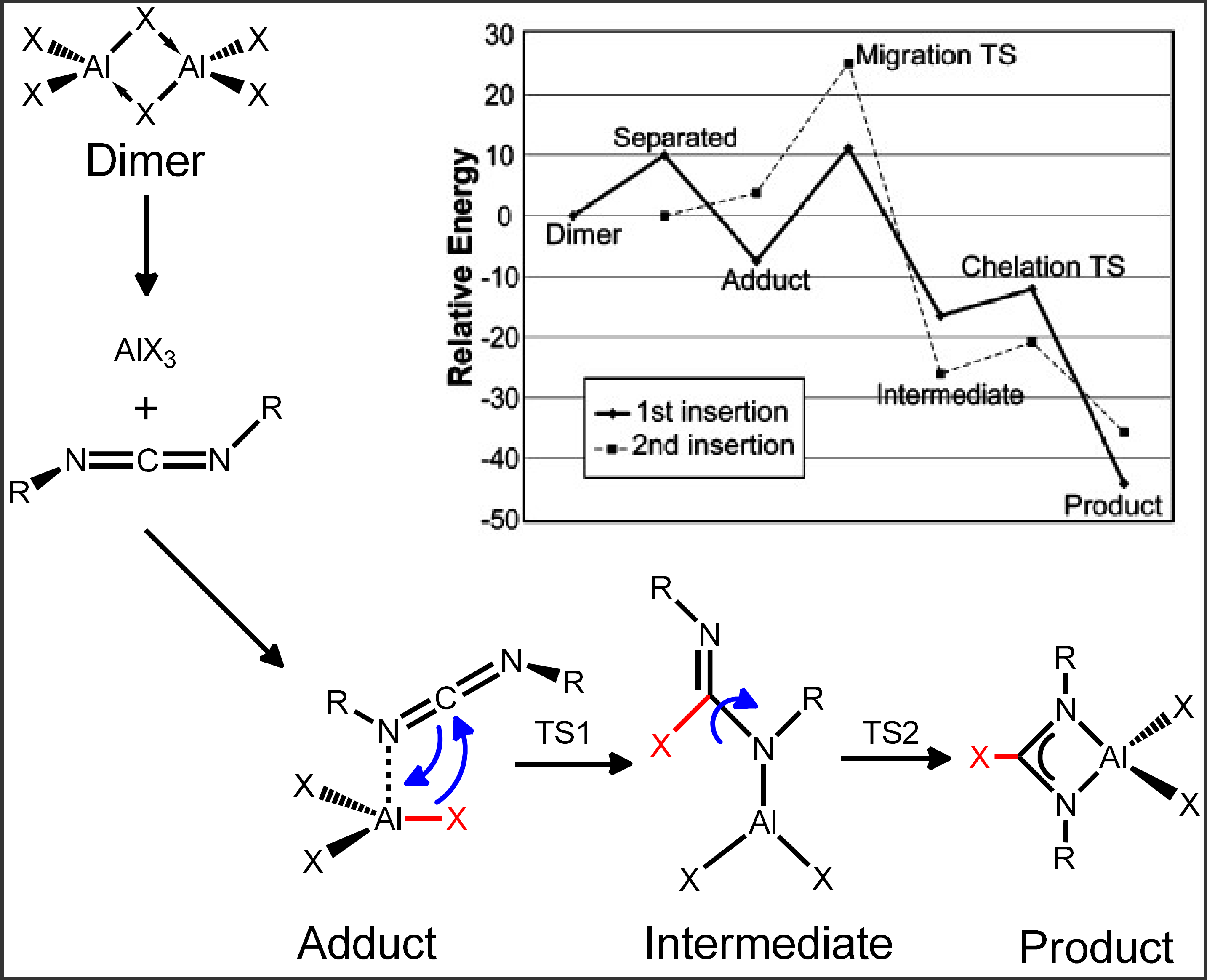
1,1 insertion – both the ligand and the metal end up on the first atom of the incoming ligand

1,2 insertion – the metal ends up on the first atom and the ligand ends up on the second atom of the incoming ligand

Three Calculated Insertions at an Al Centre



Carbodiimide Insertion



1,1 Migratory Insertion

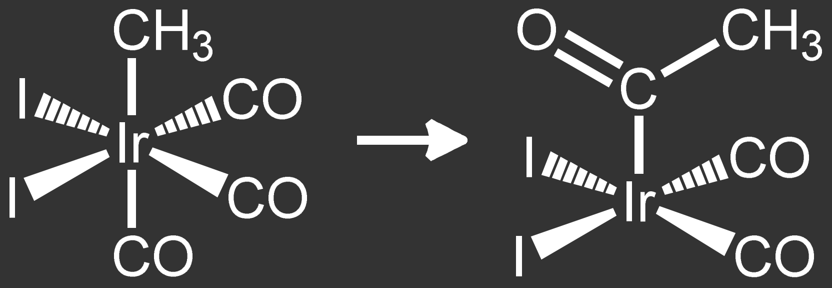
Cativa process

The Cativa process is the main acetic acid fabvrication method used today, making this from methanol and carbon monoxide.

$$H_3COH + CO \rightarrow HO\text{-}C(O)\text{-}CH_3$$

Acetic acid production

The main step is 1,1-migratory insertion:



1,2 Migratory Insertion

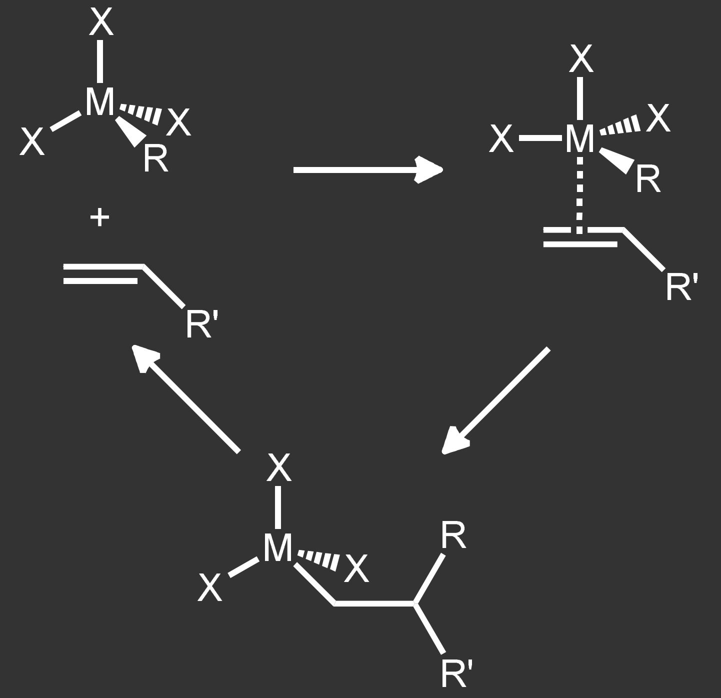
Ziegler-Natta Catalysis

Ziegler-Natta catalysis polymerizes α-olefins using a 1,2-insertion mechanism.

$$n\ H_2C{=}CH\text{-}R \rightarrow \left(CH_2CH(R) \right)_n$$

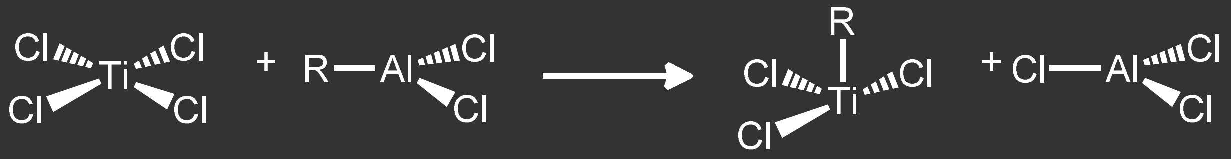
polymerization

General 1,2-insertion:

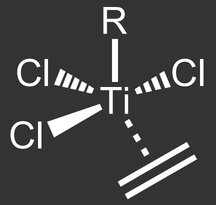


Ziegler-Natta Catalysis + Co-catalyst

In order for an organometallic species to have an open coordination site for this to proceed, a co-catalyst acid needs to pluck a ligand off of the catalyst (and possibly supply the first R group:

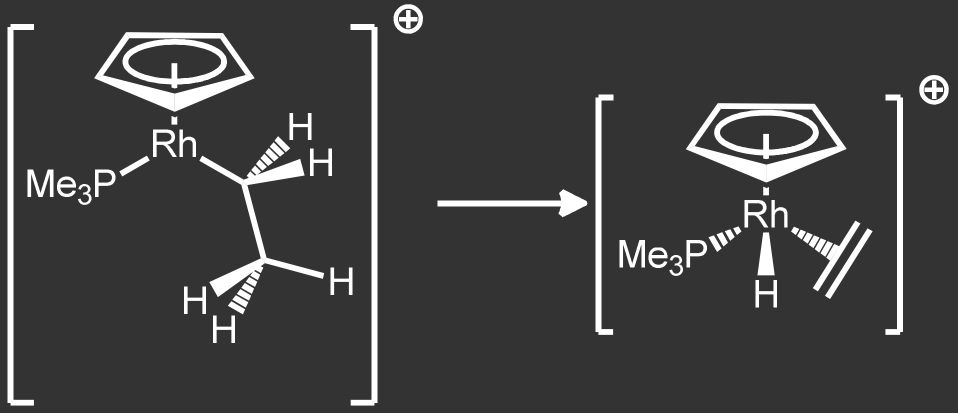


Then the metal centre is ready to start Z-R catalysis:



Hydride Elimination

A reverse of 1,2 migratory insertion, β-hydride elimination (the most common type) has the metal steal a hydrogen from the ligand (oxidising it!) to produce an alkene:



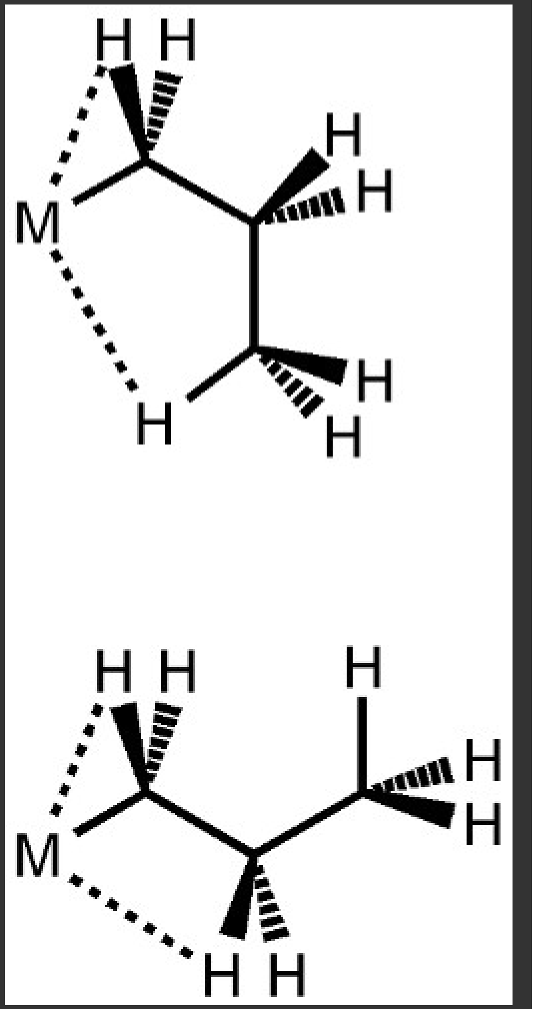
16 e^- ***18 e^-***

The driving force is often to reach an 18 electron species.

Why the Beta Position

The beta position is the easiest of the three shown for abstraction, because it is intermediate.

- The alpha position is too strained
- The gamma position is generally too far

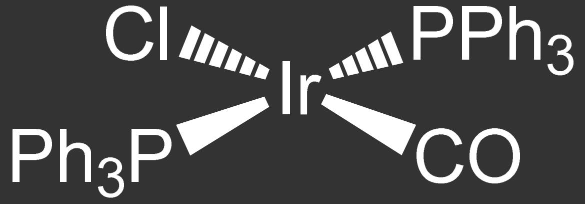


List of Inorganic Reactions

Type	***Coord. Number***	***Oxidation State***
Addition (Association)	Increase	Same
Elimination (Dissociation)	Decrease	Same
Intermediate (I_a or I_d)	Same	Same
Oxidative Addition	Increase	Increase
Reductive Elimination	Decrease	Decrease
Nucleophilic Displacement	Same	Increase
Migratory Insertion	Decrease	Same
Elimination	Increase	Same

Vaska's Complex

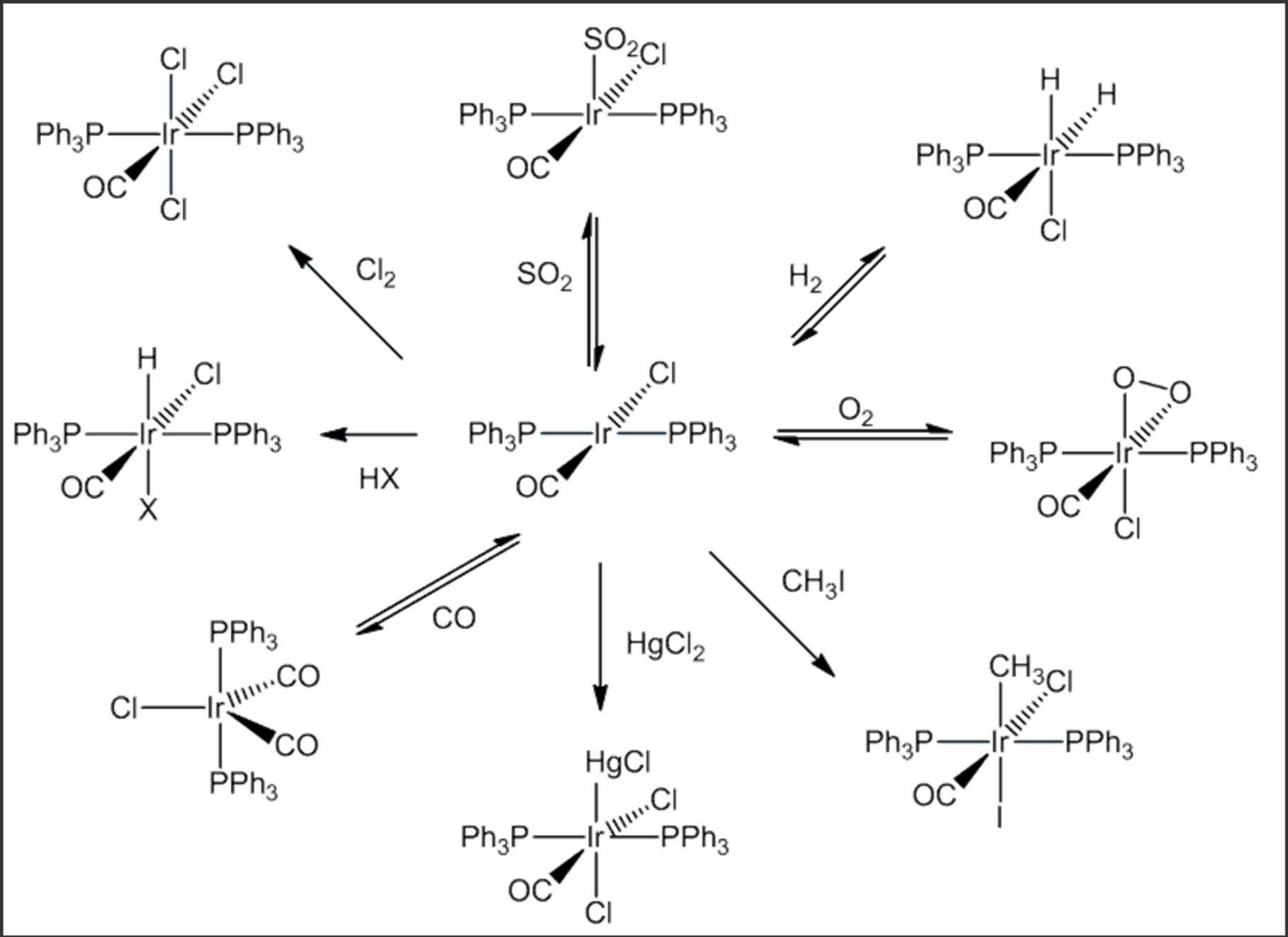
Vaska's complex is a 16 e^- species that is famous for conceptualizing the chemistry involved in homogeneous catalysis. Many of the products of reactions of Vaska's complex with small molecules are isolable and can be structurally characterised.



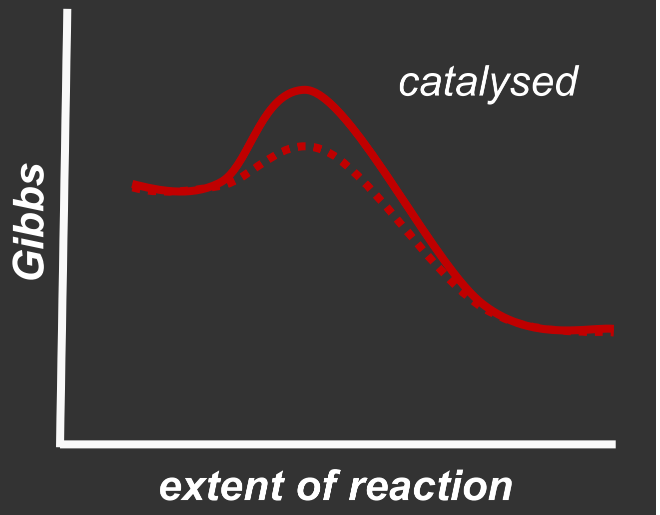
It can be tough to make:

$IrCl_3(H_2O)_3$ + 3 PPh_3 + $HCON(Me_3)_2$ + $PhNH_2$ →
$IrCl(CO)(PPh_3)_2$ + $[Me_2NH_2]Cl$ + $OPPh_3$+ $[PhNH_3]Cl$ + 2 H_2O

Vaska's Complex: Reactivity



Catalysis



Remember that the role of a catalyst is to lower the activation energy of a given, thermodynamically favourable reaction in order to make it easy and quick (*facile* and *labile*) under gentle conditions.

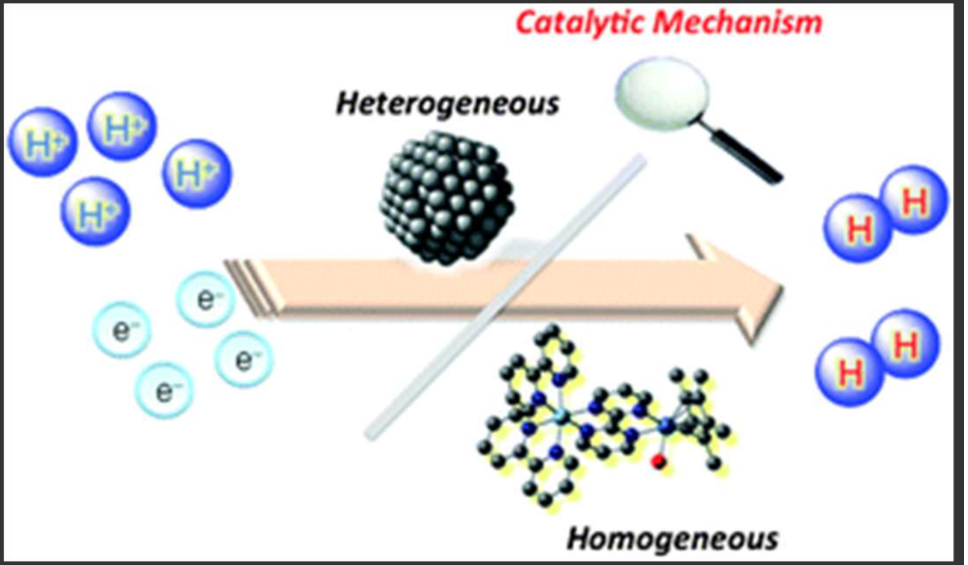
You can see that the reality of the reaction coordinate is more complicated than just lowering one activation energy.

We will generally discuss homogeneous catalysis, but there can also be heterogeneous catalysis.

Homogeneous Catalysis

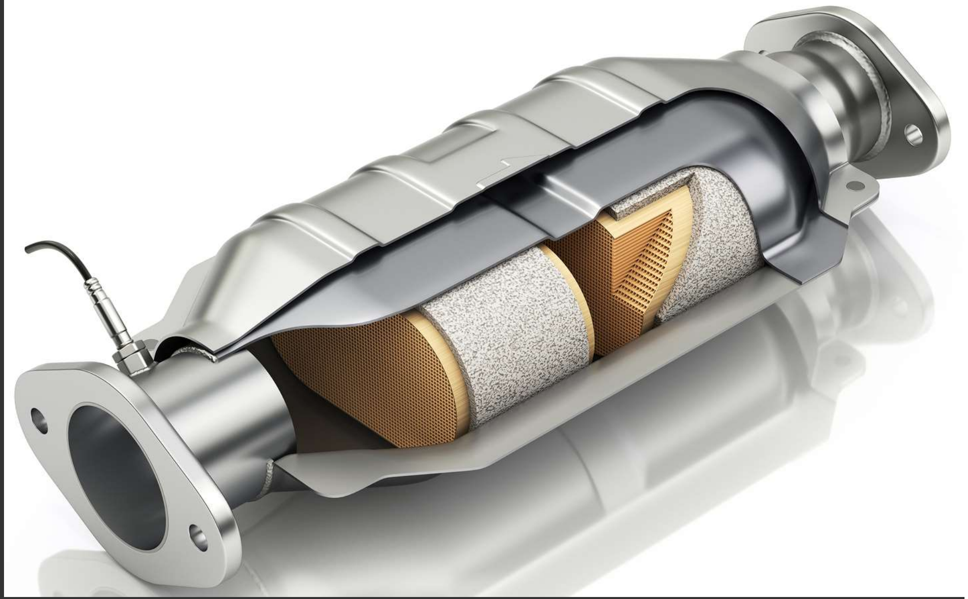
Homogeneous catalysis occurs when the catalyst and the species being acted on are in the same phase. Although this commonly occurs in solution, it is reasonable to allow this to occur in gas and solid phases as well.

Heterogeneous catalysis occurs when the catalyst and the active species are in different phases, like in the catalytic converter in a car's exhaust system.



Catalytic Converter

A catalytic converter uses Pt, Pd, and/or Rh as solid particles dispersed over a high surface area solid substrate. The metals act as a site for reduction (Rh, Pt) or oxidation (Pt, Pd) of the effluent of the combustion engine.



Reduction, NO_x to N_2:

$2\ CO + 2\ NO \rightarrow 2\ CO_2 + N_2$
$C_xH_y + NO \rightarrow CO_2 + H_2O + N_2$
$2\ H_2 + 2\ NO \rightarrow 2\ H_2O + N_2$

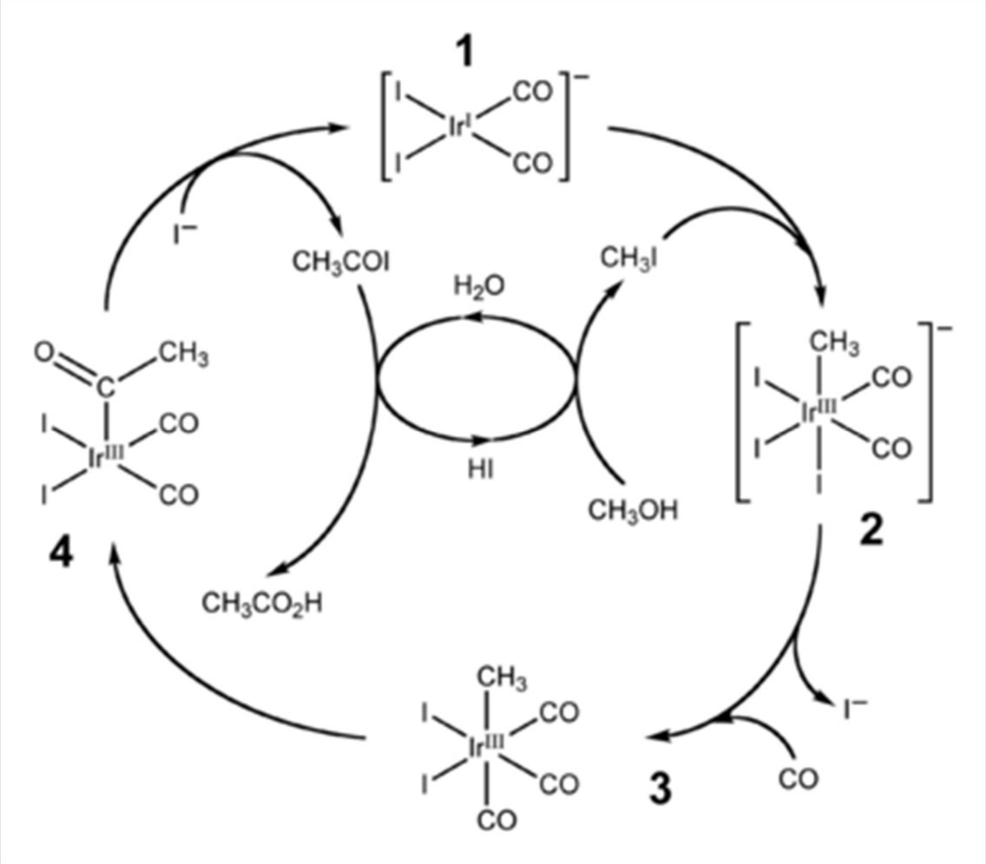
Oxidation, CO to CO_2:

$2\ CO + O_2 \rightarrow 2\ CO_2$

1,1 Migratory Insertion - Carbonylation

Cativa acetic acid process

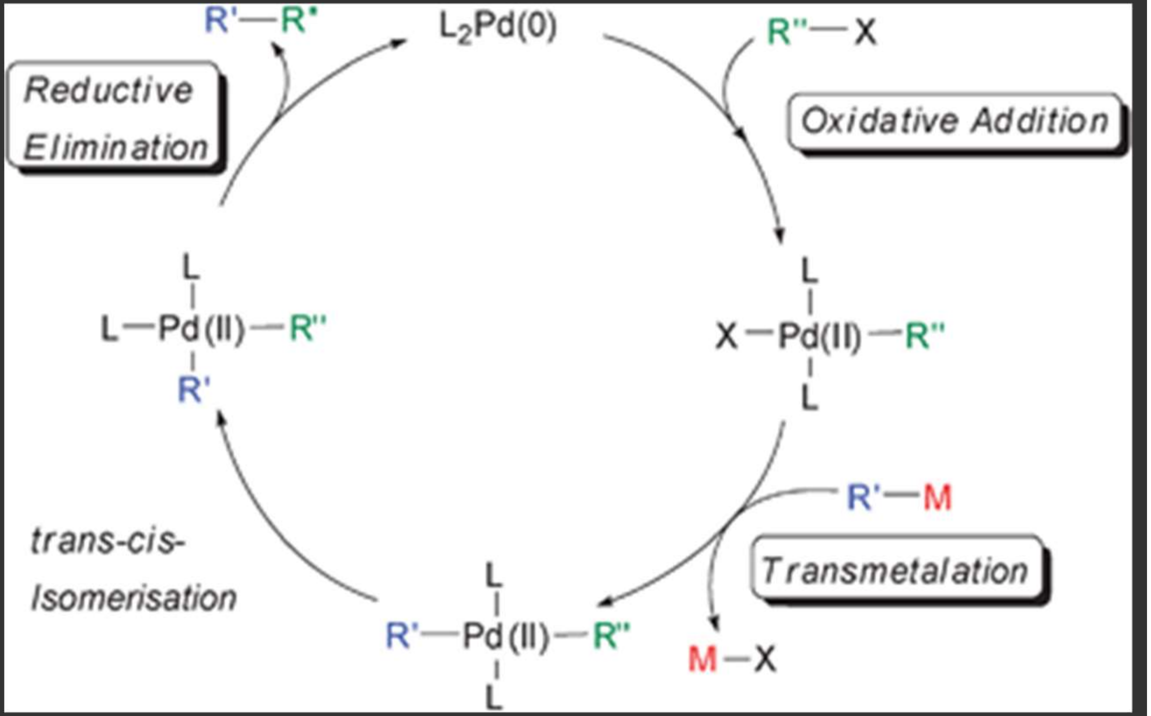
This process makes methanol and carbon monoxide into acetic acid. 6 million tonnes of acetic acid was made by this method worldwide in 2002. It has replaced the Monsanto process.



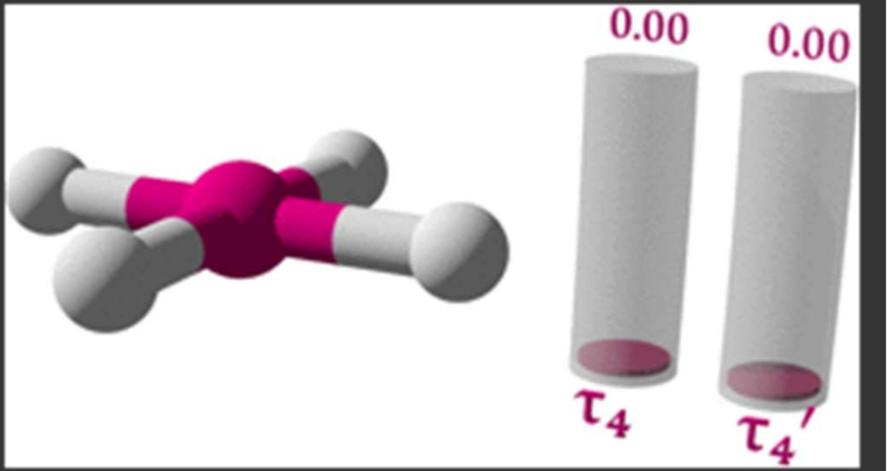
Palladium Cross Coupling

Palladium cross-coupling is a potent C-C formation catalysis method in synthetic chemistry. It involves:

1. oxidative addition
2. transmetalation
3. trans-cis isomerization
4. reductive elimination



Tau Factors: T_h vs. SqPl



A recent (2007) paper used similar logic to develop two τ parameters for 4-coordinate geometries:

$$\tau = \frac{360-\beta-\alpha}{360-2\theta}$$

$$\tau' = \frac{\beta-\alpha}{360-\theta}$$

where θ = 109.5° in a 4-coordinate system. This is a little more complicated than for a 5-coordinate system. But, τ and τ' = 0 is fully square planar, τ and τ' = 1 is fully tetrahedral.

This pseudorotation can scramble the *cis* and *trans* positions in a square planar geometry.

Transmetalation

In the case of Pd-mediated cross-coupling, many electropositive metals will have a thermodynamic driving force to exchange an alkyl for a halide:

$$L_2(X)(R')Pd^{II} + MgR_2 \rightarrow RMgX_{\text{(a Grignard!)}} + L_2(R)(R')Pd^{II}$$

Kumda coupling

$$L_2(X)(R')Pd^{II} + ZnR_2 \rightarrow RZnX + L_2(R)(R')Pd^{II}$$

Negishi coupling

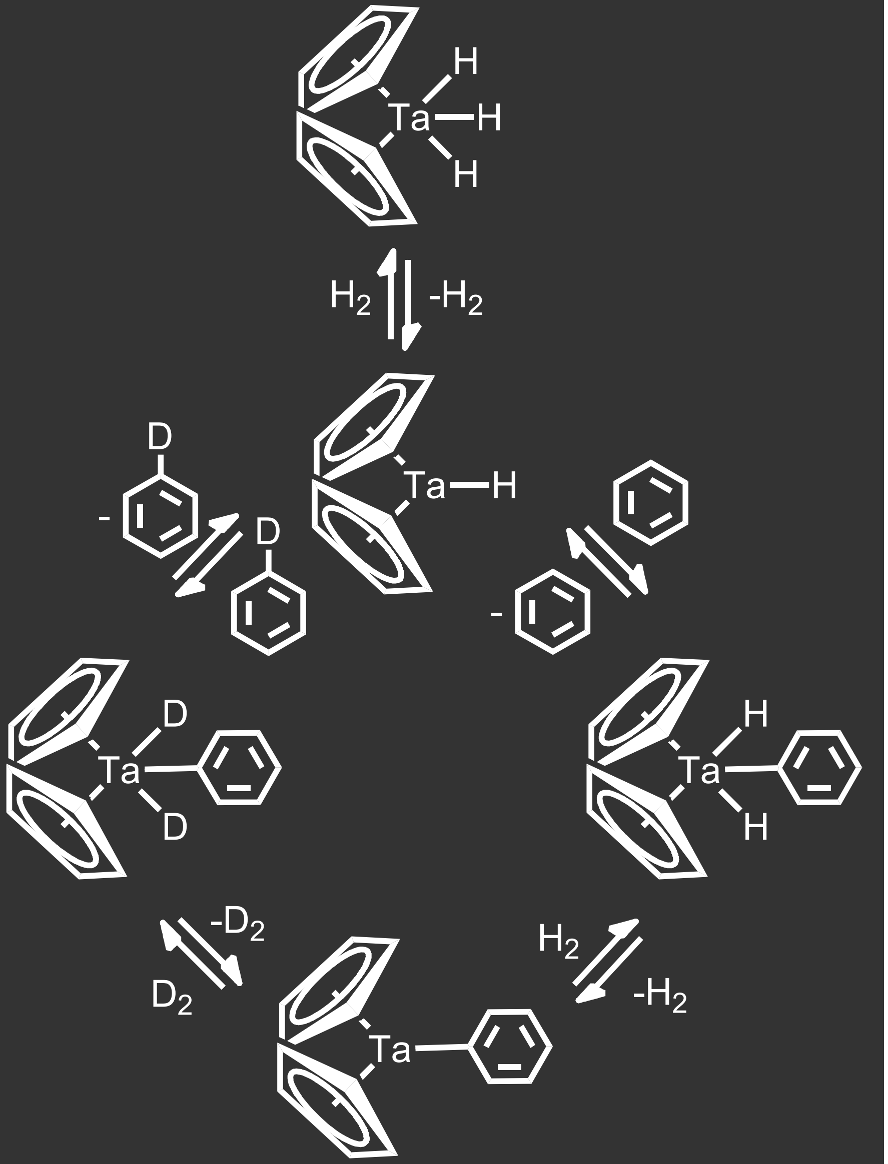
$$L_2(X)(R')Pd^{II} + BR_3 \rightarrow R_2BX + L_2(R)(R')Pd^{II}$$

Suzuki coupling

Deuteration

Deuteration is a series of oxidative additions and reductive eliminations leading to sigma bond metathesis.

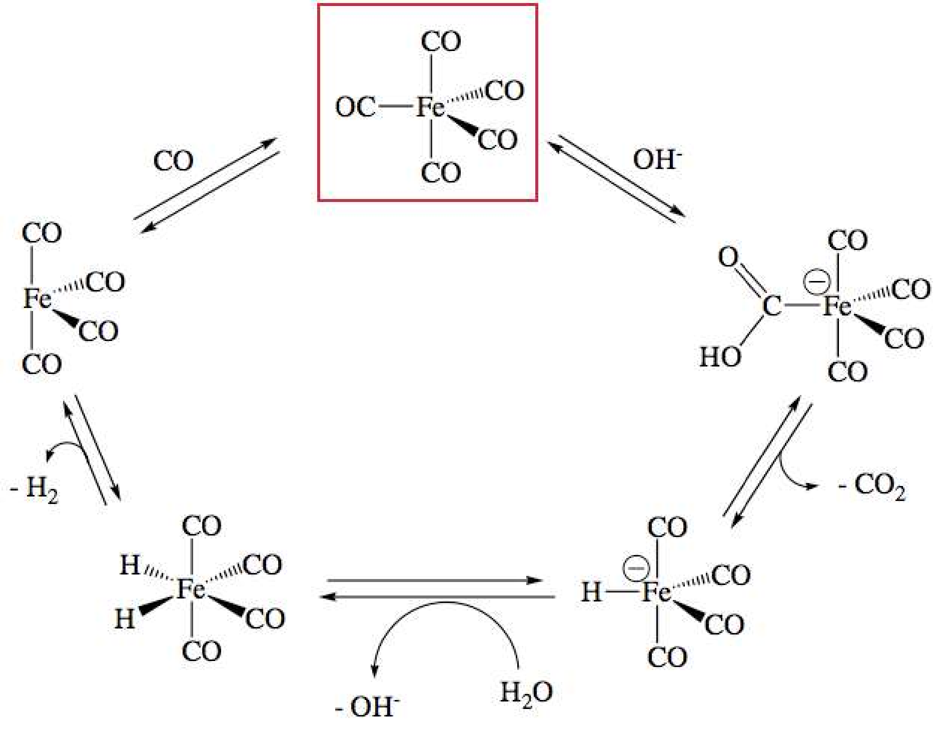
After metathesizing all of the C-H bonds on C_6H_6 with C-D bonds, benzene (for instance) can be transformed to deutero-benzene.



Water Gas Shift Mechanism

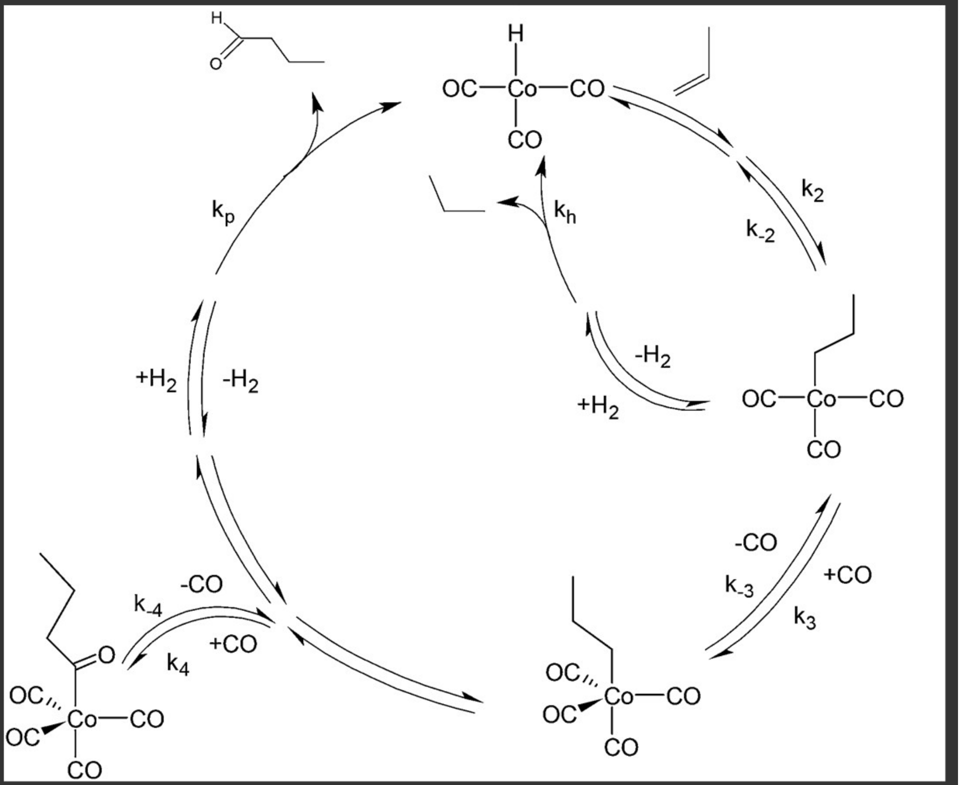
The Water-Gas Shift reaction is named this because it “shifts” the equilibrium of “water gas” (a mixture of water and CO) to H_2 and CO_2.
It undergoes:

- Nucleophilic addition
- β-hydrogen elimination
- α-hydrogen elimination (after water association)
- Reductive elimination
- CO association



$$CO + H_2O \rightarrow CO_2 + H_2$$

Hydroformylation



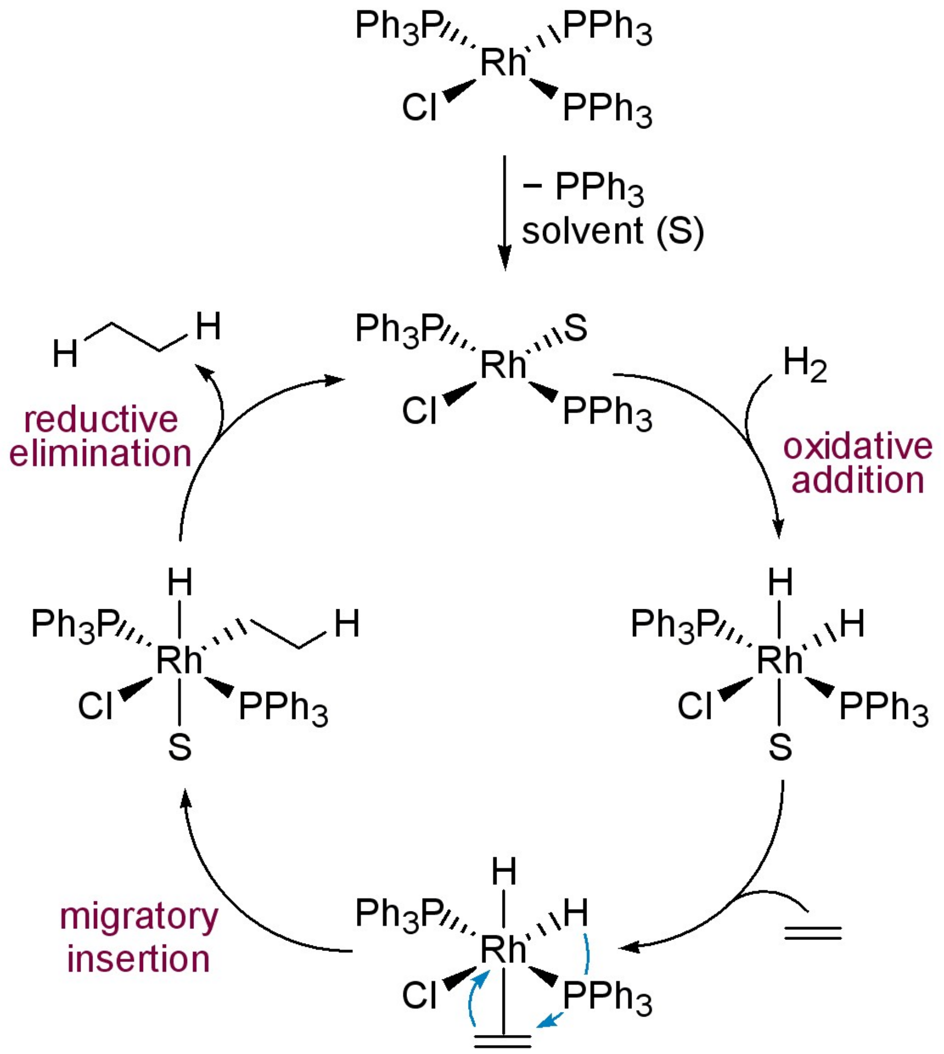
Hydrofomylation (the “oxo” process) makes an aldehyde from a parent alkene. It follows several familiar mechanistic steps:

- Alkene coordination
  - k_2 is the 1,2 migration of the hydride to the alkene (to produce an alkane)
  - If is oxidatively adds H_2, it produces an alkane, and starts over (k_h)
- k_3: CO association
- k_4: 1,1 migration of the alkane to the CO
  - If CO is added again before H_2 is added, it stops the reaction
- H_2 oxidative addition
- k_p: reductive elimination to form the aldehyde

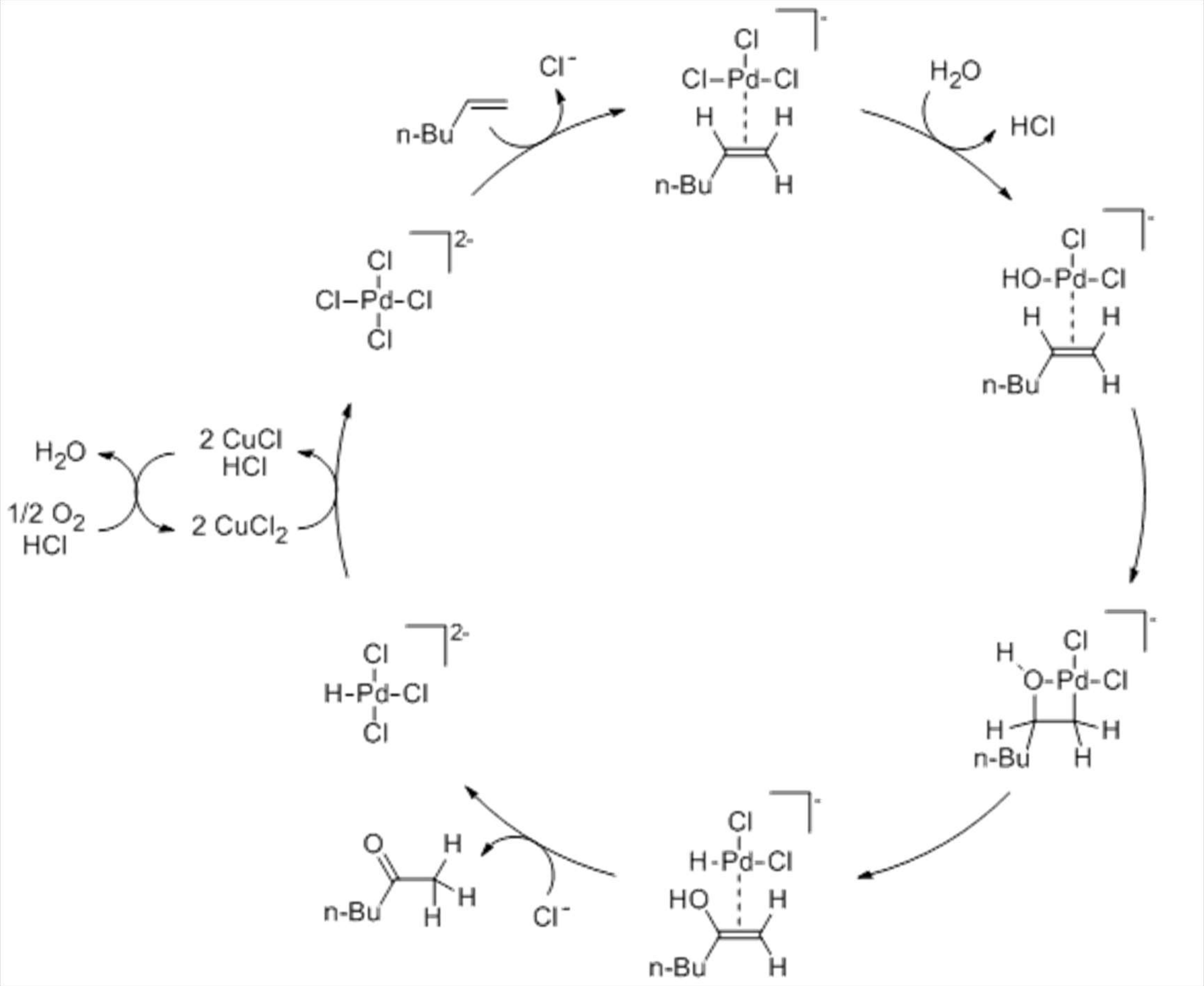
Wilkinson's Catalyst - Hydrogenation

Test yourself:

1. Does the trans effect predict this activation by solvent?
2. What type of migratory insertion is this?
3. What mechanism does the alkene coordination likely follow?

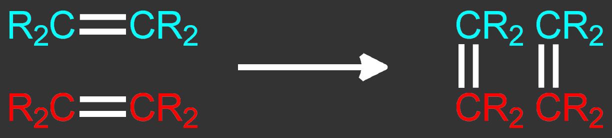


Wacker Process



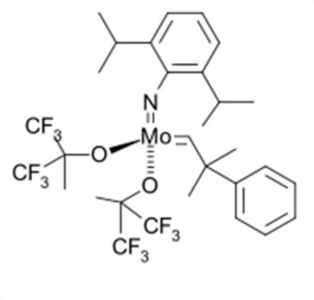
Olefin Metathesis

Olefin metathesis is beguilingly simple: you switch the ends of a double-bonded system by catalysis:

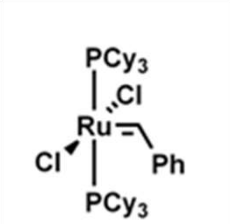


$$\begin{matrix} R_2C{=}CR_2 \\ R_2C{=}CR_2 \end{matrix} \longrightarrow \begin{matrix} CR_2 & CR_2 \\ \| & \| \\ CR_2 & CR_2 \end{matrix}$$

There are several catalysts that do this, but the Schrock's and Grubb's catalyst are the most famous:

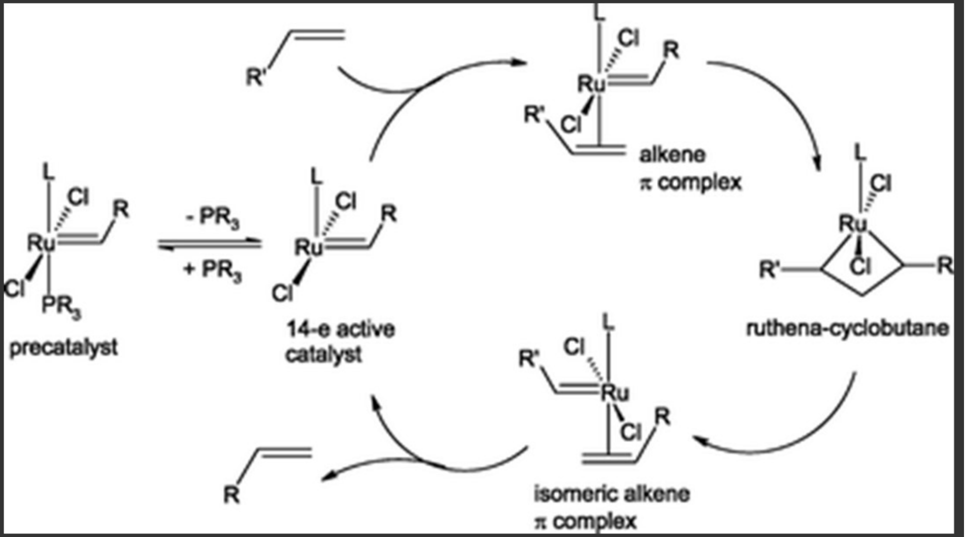


Schrock's catalyst



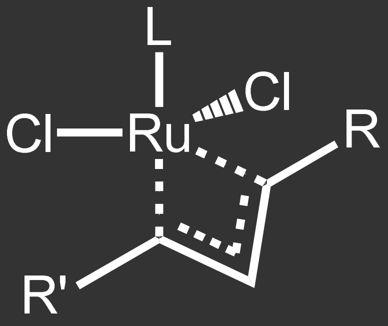
1^{st} Generation Grubbs catalyst

Olefin Metathesis



Olefin metathesis occurs by:

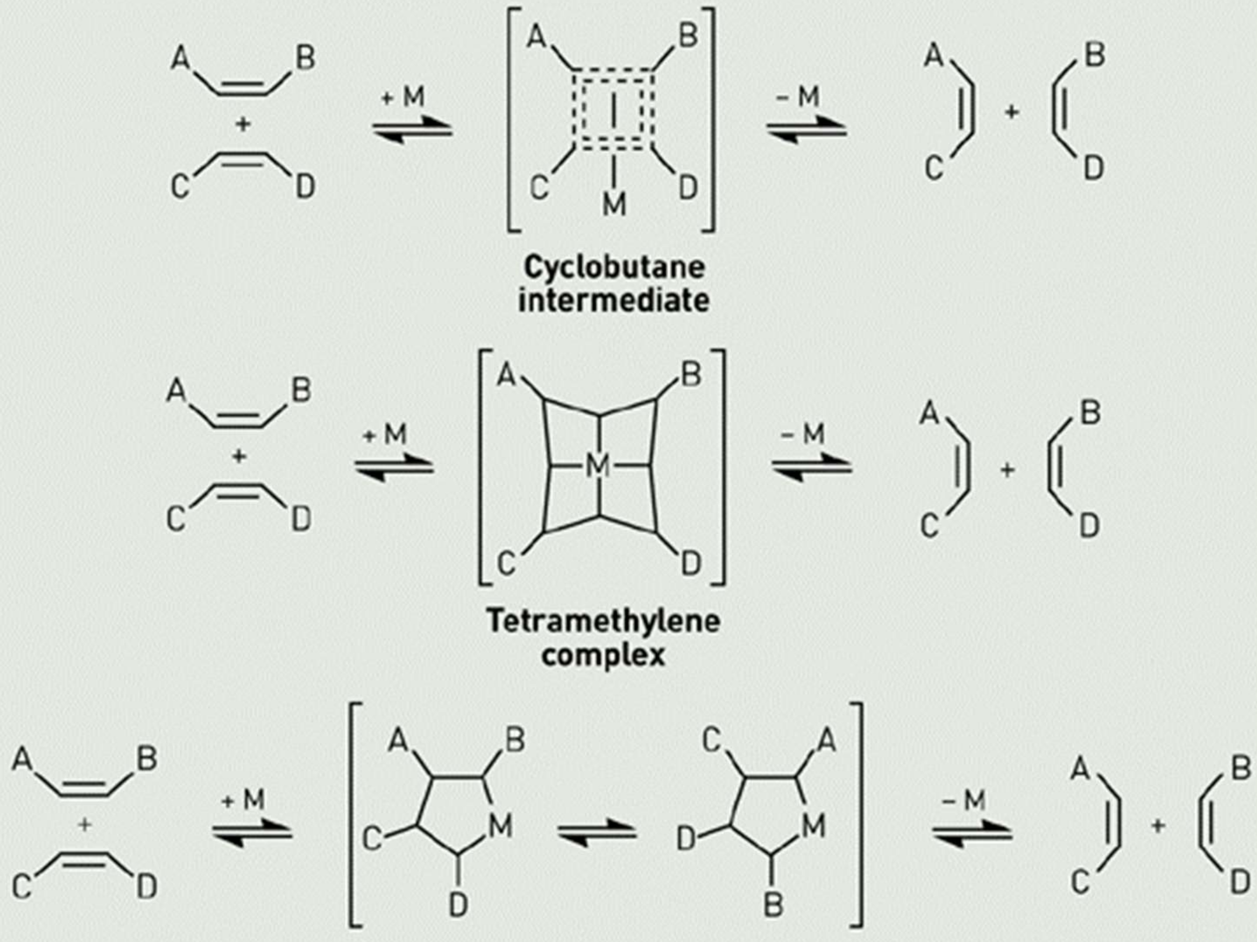
1. Ligand dissociation – to make the “active catalyst”
2. Alkene association
3. “2+2” cycloaddition – this uses the same naming as migration. The olefins each add to the other in the #2 position.
   This cyclo addition was highly contentious, and a variety of pathways were suggested, tested, and then rejected.
4. Olefin exchange
5. Olefin dissociation



It ISN'T Two Olefins!

WRONG TURNS

Unusual intermediates proposed initially have since been rejected



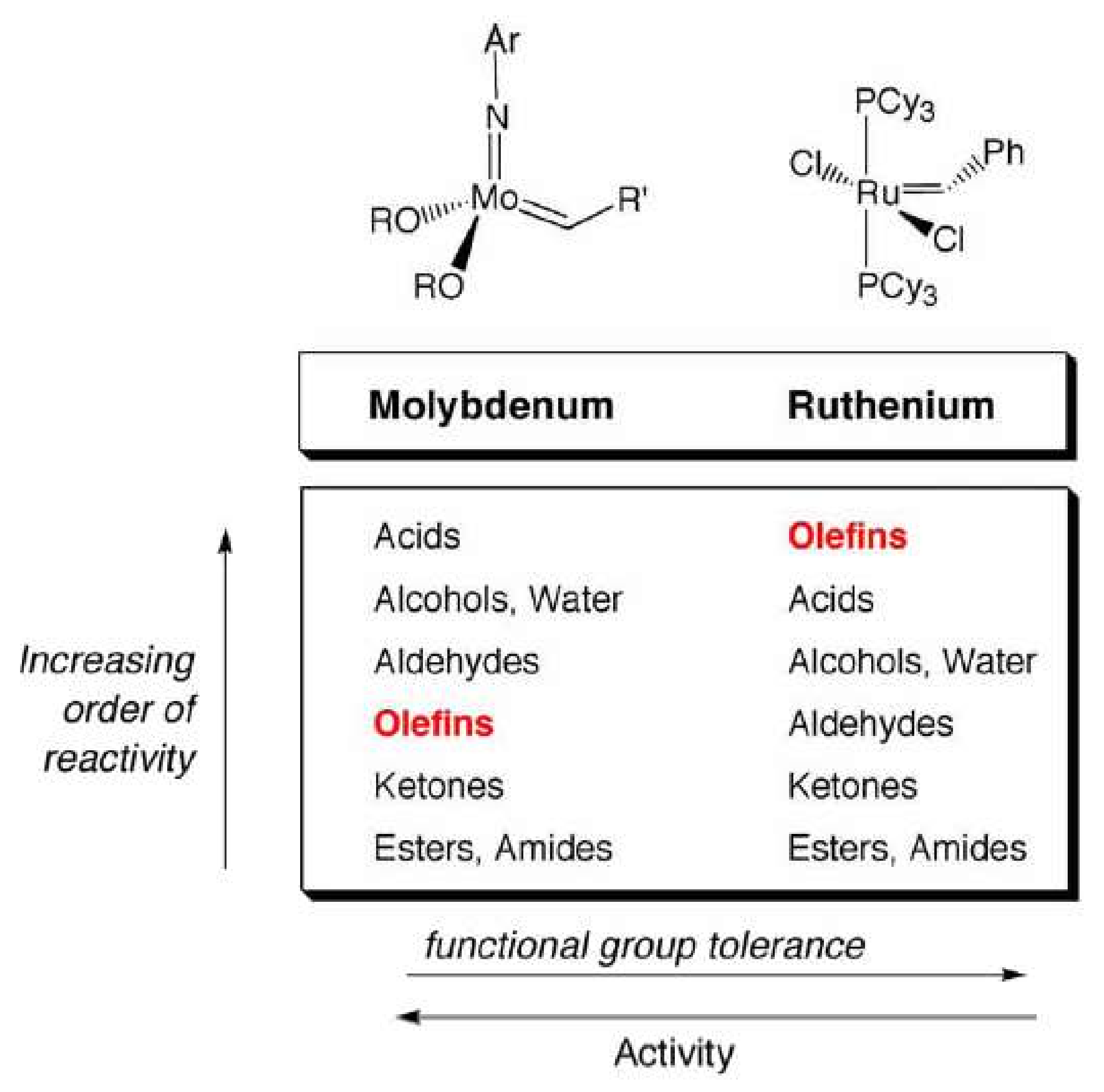
Cyclobutane intermediate

Tetramethylene complex

M = metal

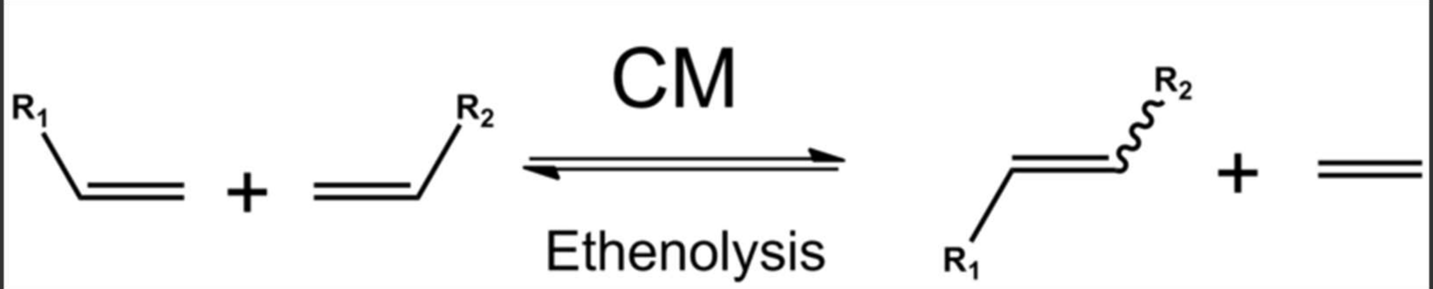
Rearranging metallacyclopentane

Comparison of Systems



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

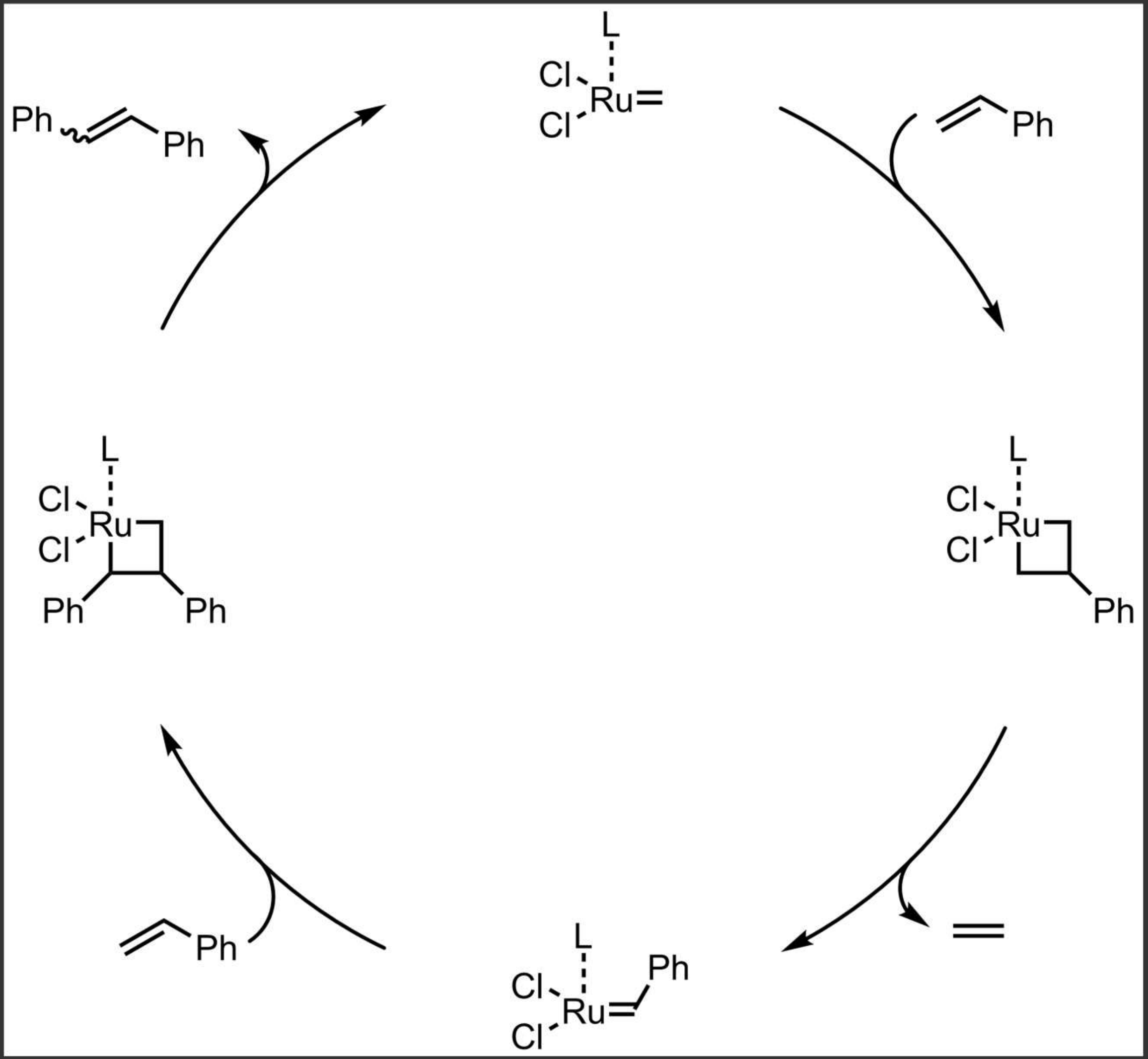
Applications – Cross Metathesis



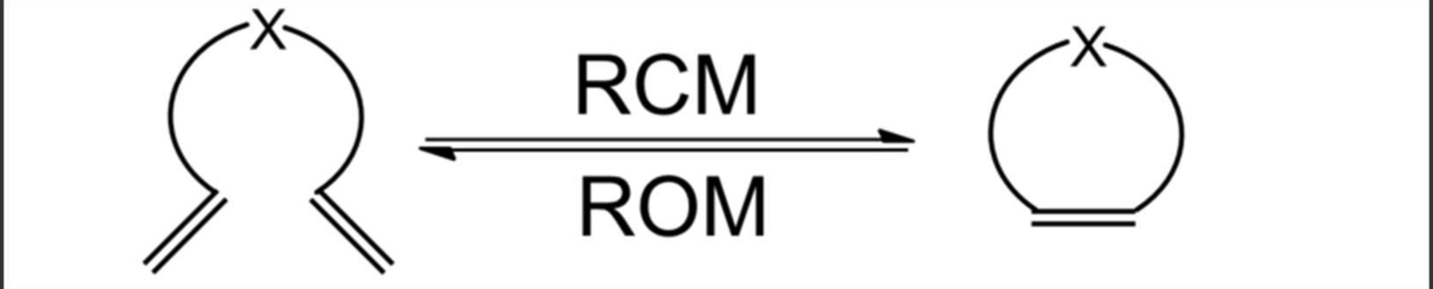
Cross metathesis can be driven forward by the evolution of ethene, which can leave the solution as a gas. This gives the reaction a Le Chatelier’s force to go forward.

If you over-pressure the solution with ethene, you can drive the reaction backwards.

Cross Metathesis Mechanism



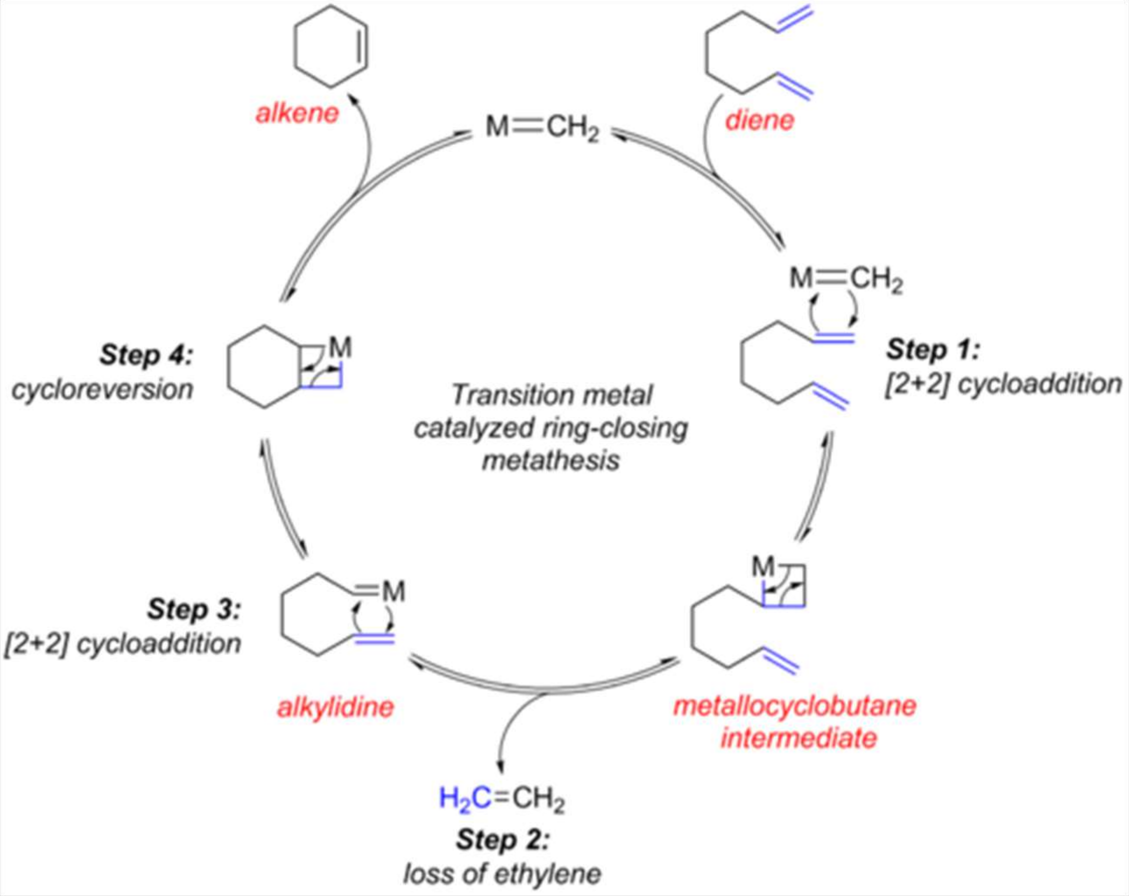
Ring Closing and Opening (Metathesis)



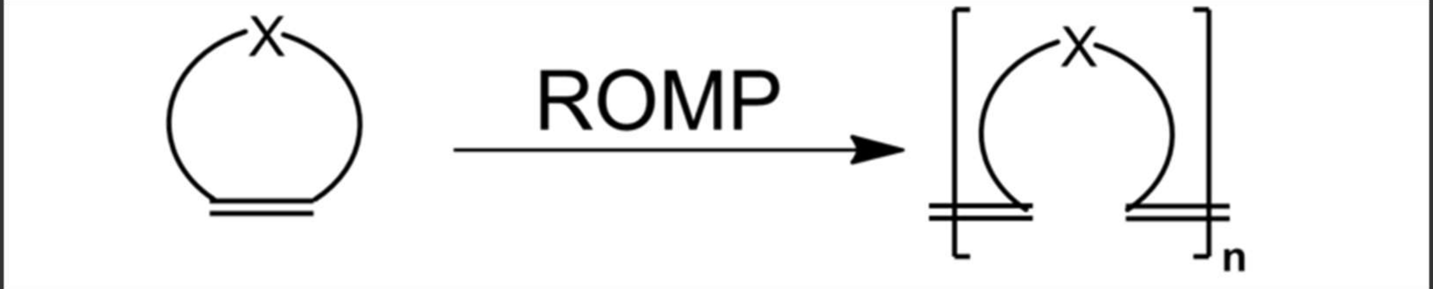
Ring closing and opening can be driven by many different chemical forces (e.g., precipitation/volatilization of one or the other component), but ring strain can play a big role.

For ring opening, you would need an olefin (e.g., ethane) to provide the “cap” for the open double bonds.

Ring Closing/Opening Mech.



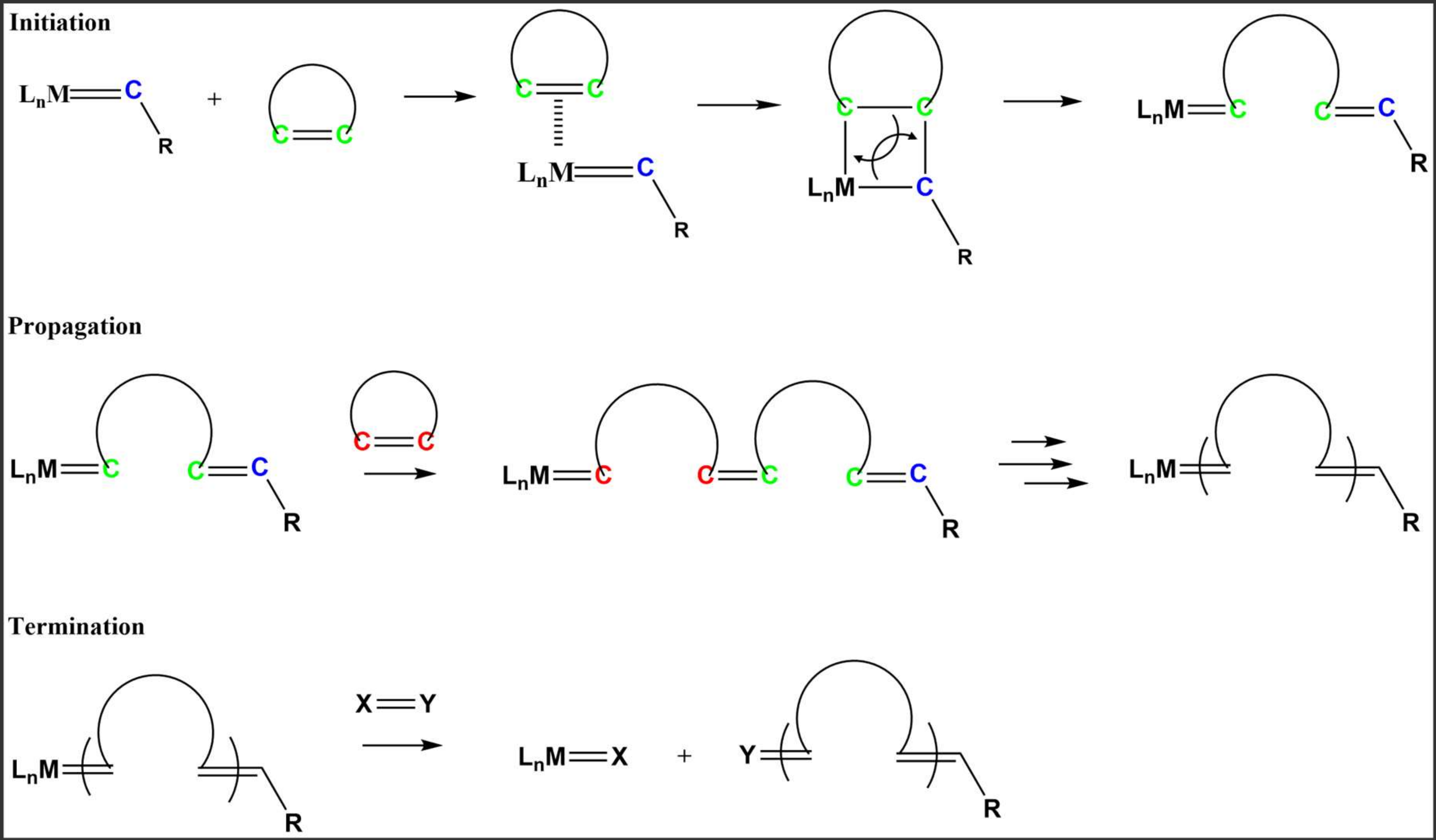
Ring Opening Polymerization



In the absence of another olefin, ROM will polymerize the open rings (ROMP!). When undertaken on a diene that is not a ring, it is called acyclic diene metathesis (ADMET).

ADMET, of course, produces ethene.

ROMP Mechanism

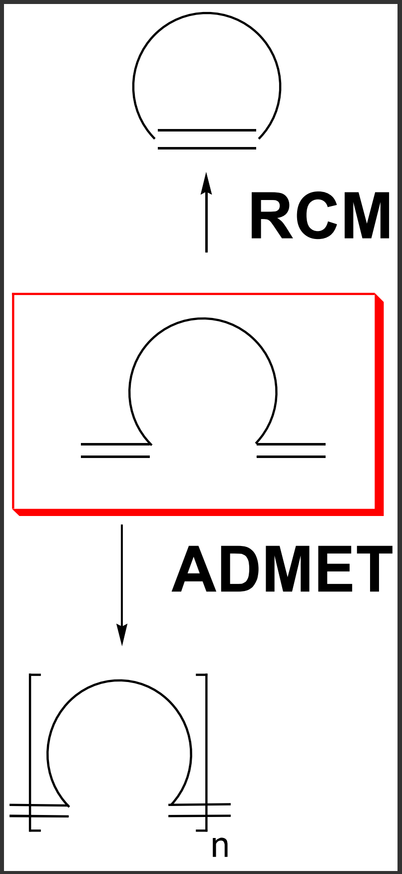


RCM Protocol

biasing reactions toward cyclization

Classical stoichiometric reaction:

Favour intramolecular ring-closing with “Ziegler” conditions (“infinite dilution” -- infuse diene at the same rate that it cyclizes)

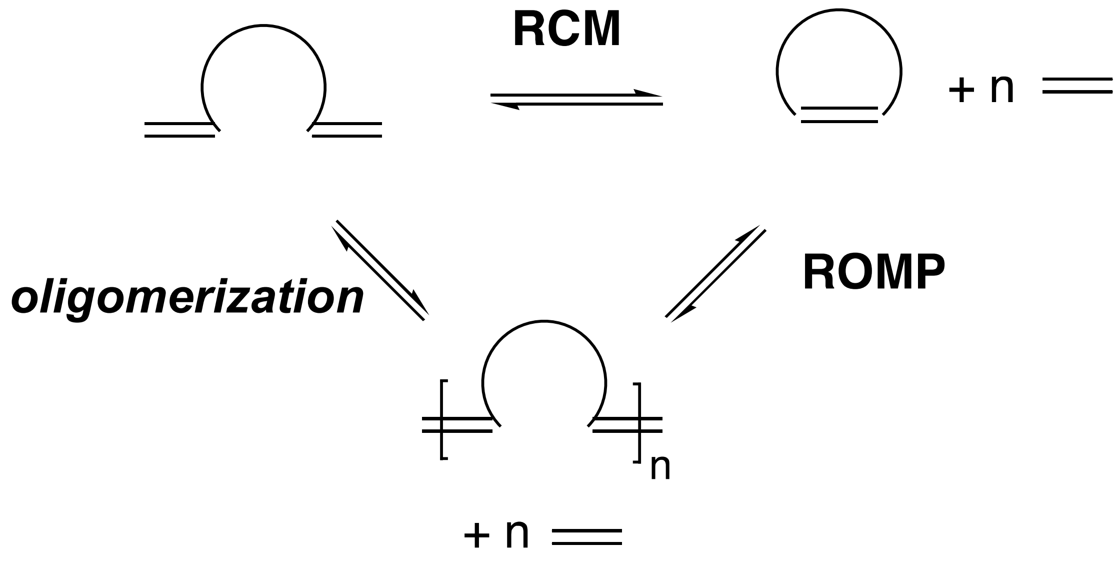


High dilution

High concentration

Reversible Metathesis?

- Metathesis often described as fully reversible…



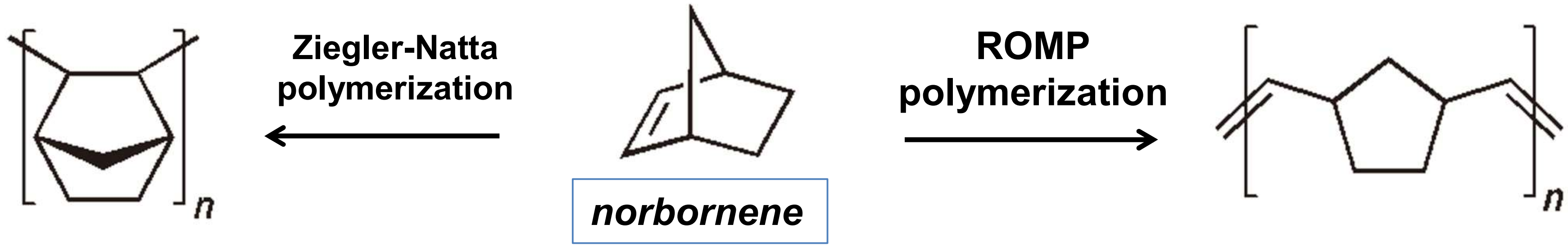
This does not take into account volatility of ethylene. Loss of C_2H_4 is irreversible under normal operating conditions.

C_2H_4 solubility in toluene (1 atm C_2H_4)

0 ˚C	95 mM
20 ˚C	45 mM
30 ˚C	25 mM
45 ˚C	**<1 mM**

Lee et al. Fluid-phase Equilibria 2005 *231*, 221

ROMP materials derived from norbornenes



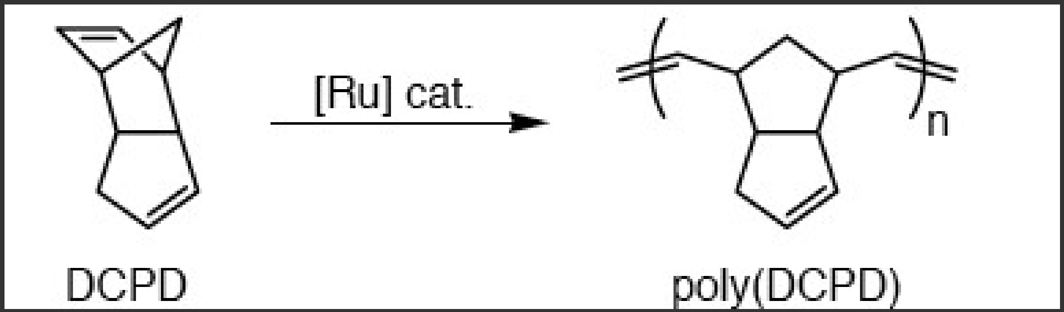
Ziegler-Natta polymerization

norbornene

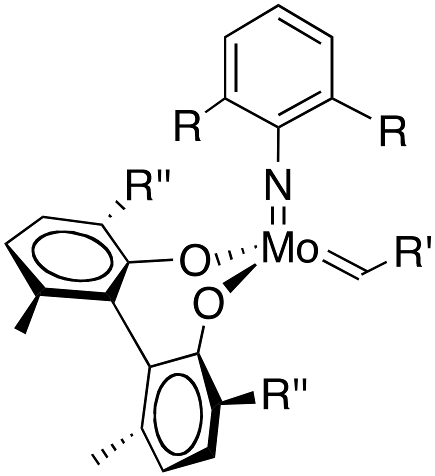
ROMP polymerization

cis + trans C=C: inhibits crystallization

C=C confers "bounce": damps vibration



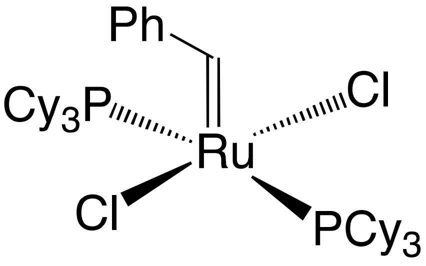
“Well-Defined” Metathesis Catalysts



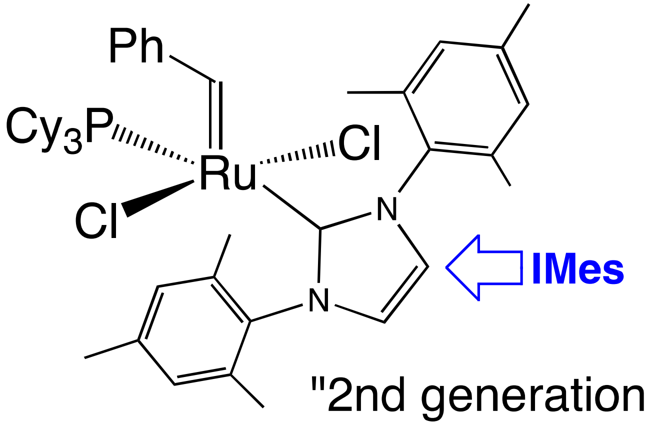
Schrock

Enabled Organic Applications

- biphen / binaphtholates
- bulky ancillary ligands:
  - limit bimolecular deactivation
  - tunable: chiral metathesis
- highly sensitive catalysts



"Grubbs I"

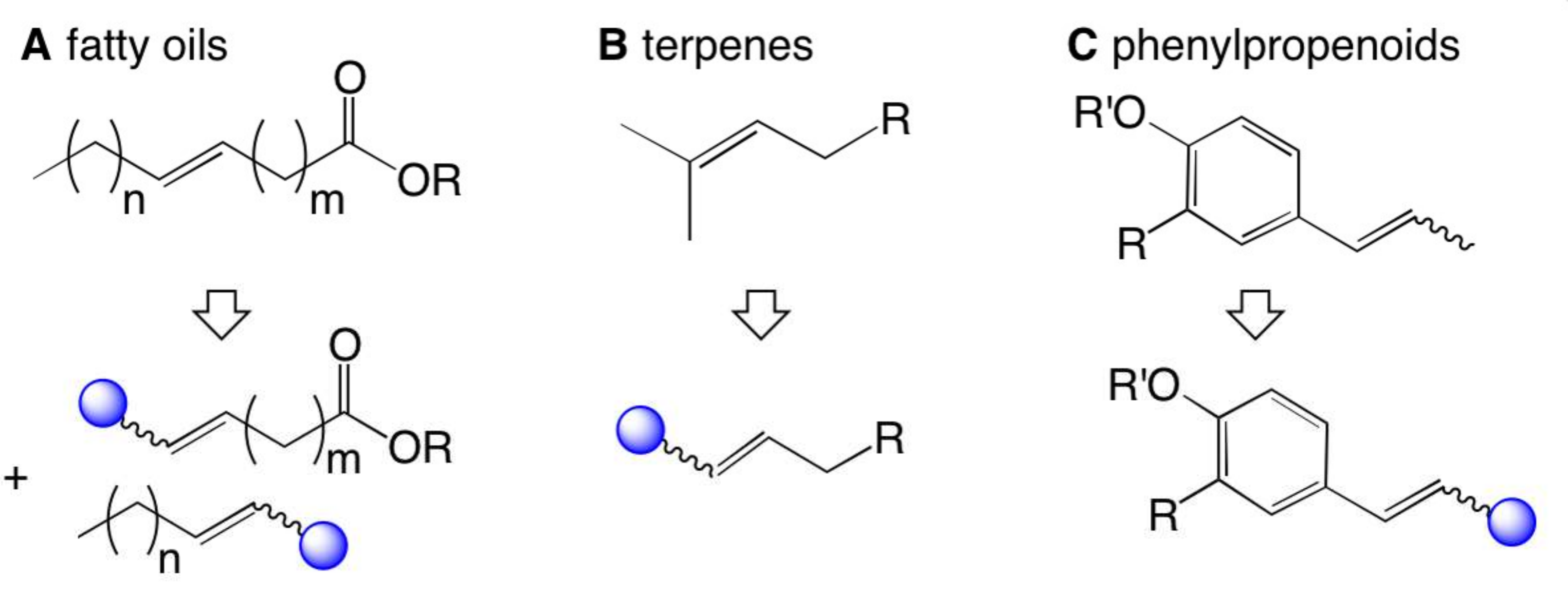


"2nd generation"

- tolerant of air, water, polar functional grps
- rich catalytic chem: tandem catalysis
- short lifetimes low selectivity

Cross Metathesis of Renewables

Adding Value to Plant Oils



1. CM with ethylene
   - *Elevance: a-olefins from palm oil*
2. Add α-functionality
   - *X = CN, CO_2R*

Challenge: low TON

Need 50,000 or higher

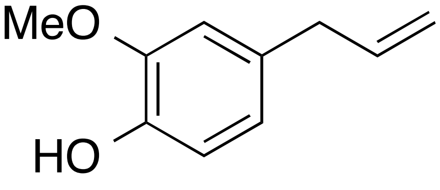
Currently... a few thousand

Higman, Lummiss, Fogg, *Angew. Chem.* **2016** 3552
Meier, *Green Chem.* **2007**, *9*, 1356
Dixneuf, *Green Chem.* **2011**, *13*, 2911

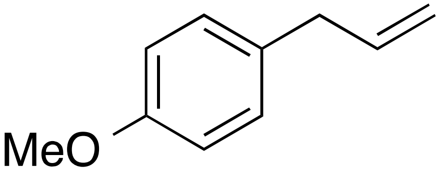
Acrylate Metathesis

high-value molecules from essential oils

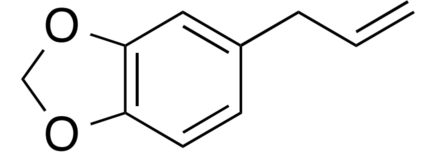
- fine chemicals by cross-metathesis of renewable arylpropenes
- capture functional groups that are costly to build into petrochemicals



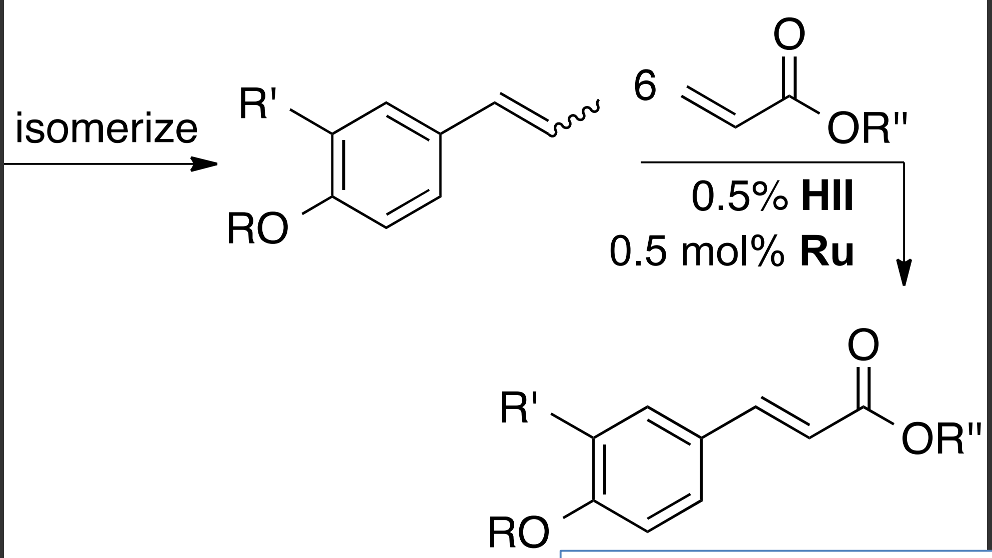
clove leaf oil (90%)



basil oil (85%)



sassafras oil (90%)

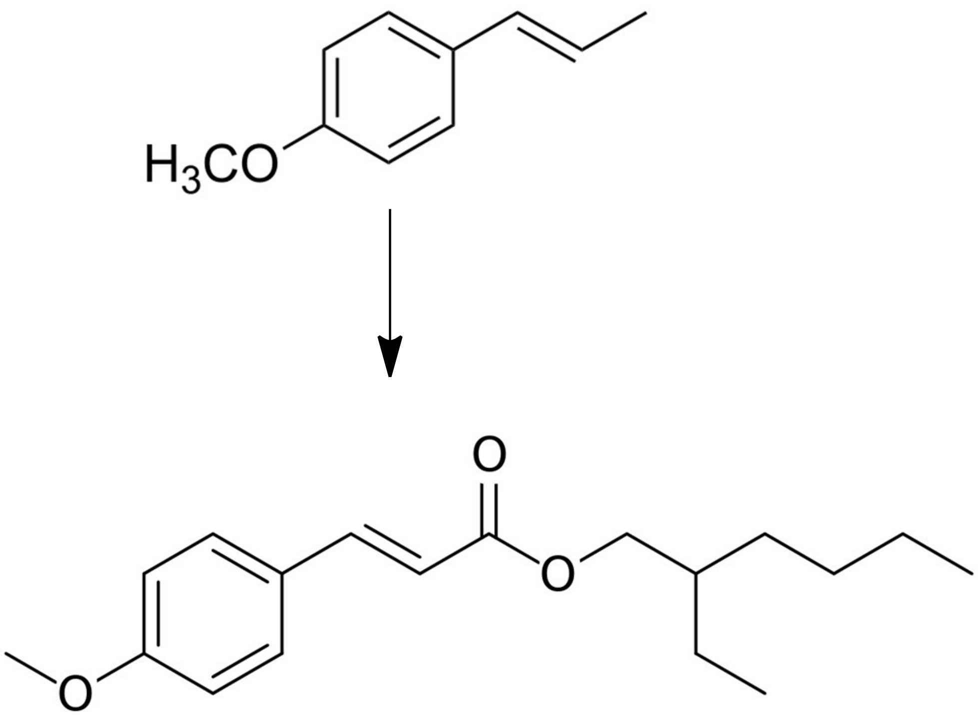


Cinnamates & Ferulates

• fragrances • sunscreens
• antioxidants • cosmetics
• pharmaceuticals

Lummiss, dos Santos, Fogg, *et. al. JACS* **2012**, *134*, 18889

Value-added Cinnamates

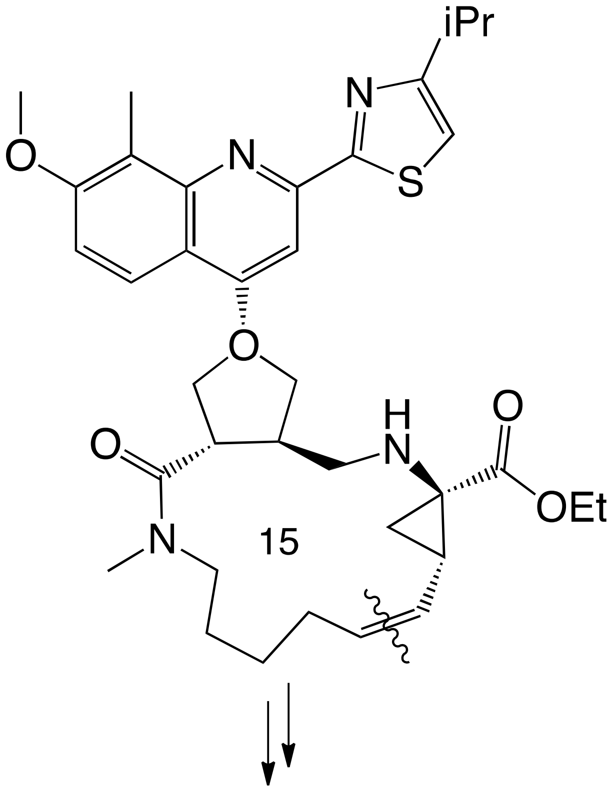


UVB-blocker / sunscreen
$1,000 / kg (Aldrich)

- challenging CM reaction
- max. TON at 100% yield = 200
- many challenges to work out for implementation of CM in industry
- need high-value targets to pay for costs

RCM in Pharmaceutical Manufacturing

- Breakthrough advances: macrocycles via RCM
- big enough to inhibit peptide-peptide interactions: small enough for oral bioavailability
- complementary to Pd X-coupling: *no longer need* preinstalled X, M



Simeprevir

Hepatitis C Virus inhibitor

2014: Simeprevir
(Johnson & Johnson)
- first commercial RCM process

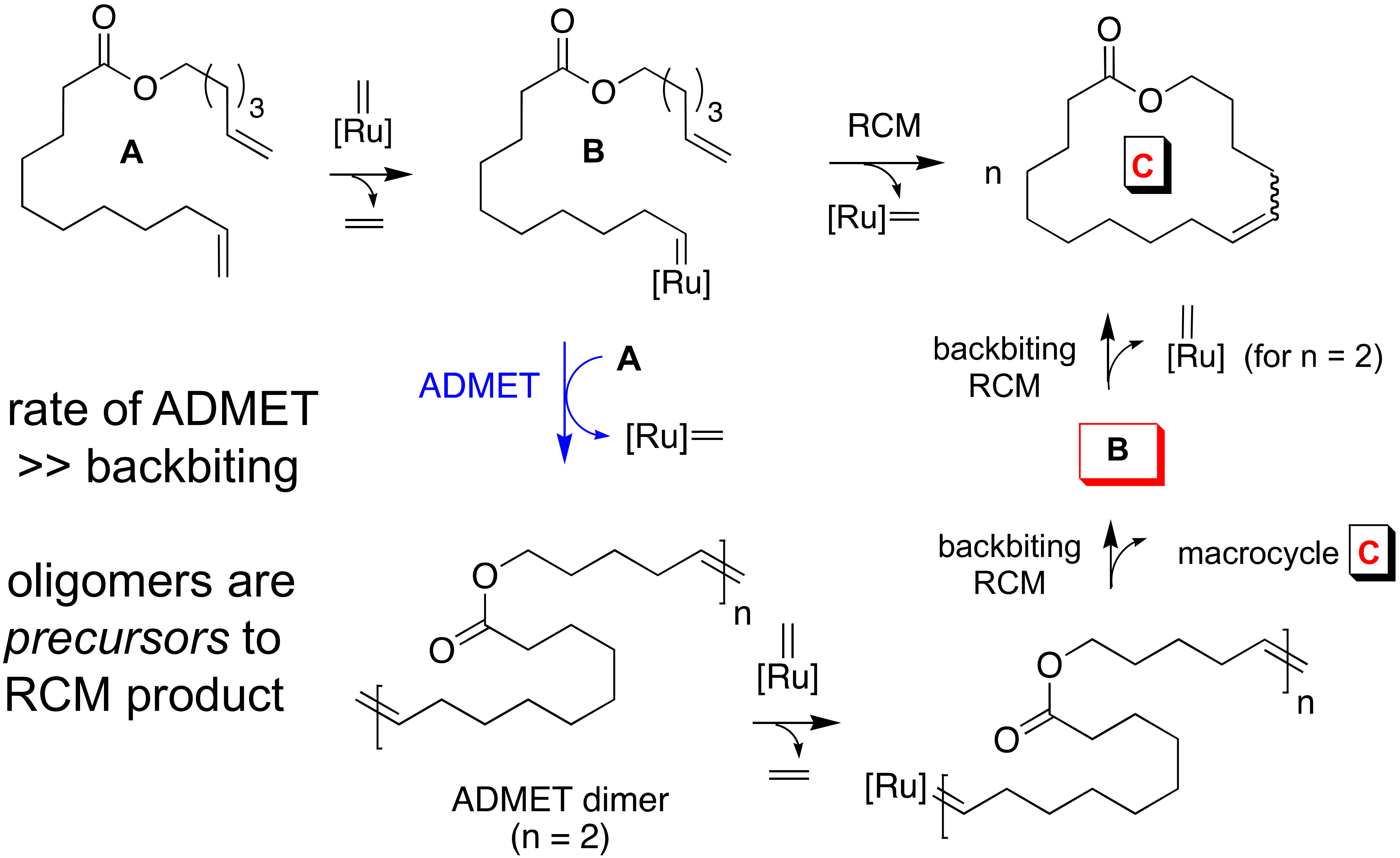
2015: Paritaprevir
(AbbVie)

2015: Vaniprevir
(Merck)

Company	**Ring size**
Boehringer-Ingelheim	15
Janssen	15
Merck	15-20
Novartis	14-17
Pfizer	28
Roche	15
Tibotec Pharma	12, 15
Aileron	>12

Higman, Lummiss, Fogg, *Angew. Chem. Int. Ed.* 2016

Indirect path,diene to macrocycle



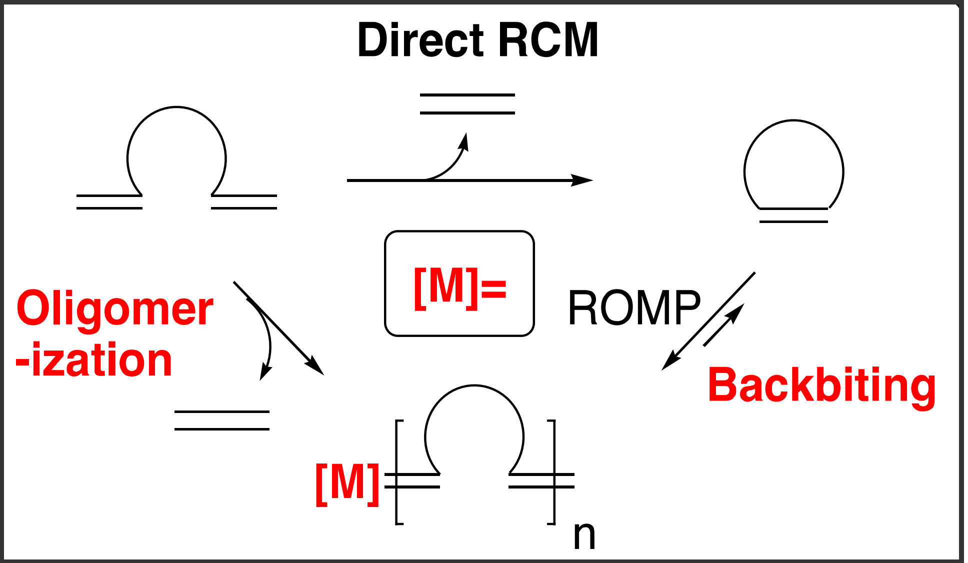
- rate of ADMET >> backbiting
- oligomers are *precursors* to RCM product

Is High Dilution Required?

Concentration-dependent ring-chain equilibria: Jacobson-Stockmayer theory

Direct RCM is favoured at high dilutions by translational entropy.

Oligomerization is favoured at high concentration by conformational/rotational entropy of the backbone.



For macrocyclic rings, oligomerization is kinetically preferred for the reactive Ru catalysts.

Thus, Ru-oligomer system has to reach equilibrium and the catalyst must live long enough to promote backbiting.

(*J. Chem. Phys.* 1950, *18*, 1600)