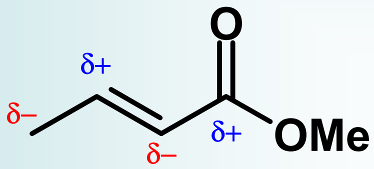
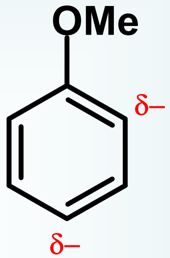
Organometallics in Organic Synthesis

1. So who cares (i.e., why?)

-Pattern of reactivity of organic compounds is imposed on molecule by existing functional groups





- By default, this limits what you can do with the compound

- Coordination of a metal fragment can change this completely

i.e., can render – an electrophilic species nucleophilic

- a nucleophilic species electrophilic
- can make a normally unstable molecule stable
- can make a stable molecule reactive
- can make impossible reactions possible

The (Very) Basics of Organometallics

-The 18 Electron Rule

Most (middle) transition metal complexes prefer having

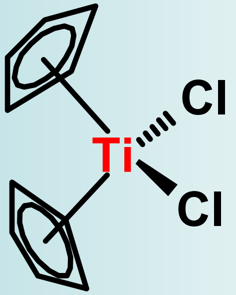
18 valence electrons (2s + 6p + 10d)

For transition metal complexes in the 0 oxidation state

4e	5e	6e	7e	8e	9e	10e
Ti	V	Cr	Mn	Fe	Co	Ni
Zr	Nb	Mo	Rc	Ru	Rh	Pd
Hf	Ta	W	Re	Os	Ir	Pt

-The 18 e rule is followed most closely in complexes of middle transition metals (Cr to Co)

-As for early transition metal complexes, it's usually too difficult to get enough ligands around the metal to get it to 18 e (i.e., Ti)



(16 e) (Cp_2TiCl_2)

- As for late transition metal complexes (Ni, Pd, Pt), particularly the square planar $M^{II}L_4$ complexes
  - tend to be very stable as 16 e^- complexes

    - energy gap to 9th orbital is quite big; molecule is quite willing <u>not</u> to fill that orbital

To count to 18 (or 16), need e^-'s from ligands

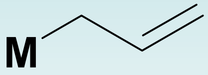
- I'll adopt a 'radical approach' – **not only valid one**

A) Inorganic Ligands

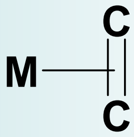
$1e^-$	**-X**	**-H**	**-R**	
$2e^-$	**R_3P:**	**$(RO)_3P$:**	**R-C≡N:**	**R-N≡C:**
	R_3N:	**R_2S:**	**R_2O:**	
$3e^-$	**NO (usually)**	**nitrosyl complexes**		

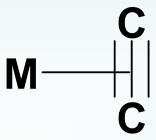
Organic Ligands - Part 1

η^1 (1 e^-) -R (alkyls) -Ph (aryls)


(σ -allyls)

η^2 (2 e-)

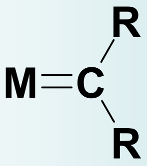
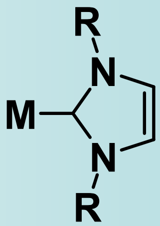

(alkenes)


(alkynes)

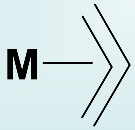
η^1 (2e^-)

$$\overset{-}{M}-C\equiv\overset{+}{O} \longleftrightarrow M=C=O$$

(carbonyl ligands)



(carbenes, alkylidenes)

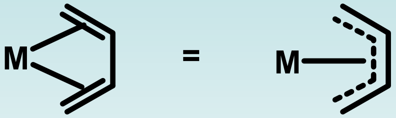
η^3 (3e^-)


(π -allyls)

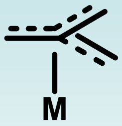
η^1 (3e^-) $M\equiv C-R$ (carbynes)

Organic Ligands, Cont'd.

η^4 (4e$^-$)

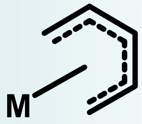


(dienes)

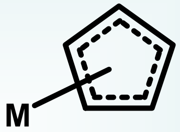


(trimethylenemethanes)
(TMM)

η^5 (5e$^-$)

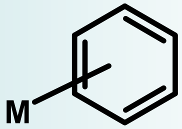


(dienyls)



(cyclopentadienyls)

η^6 (6e$^-$)

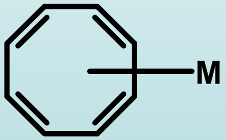


(arenes, trienes)

η^7 (7e$^-$)

(trienyls)

η^8 (8e$^-$)



(cyclotetraenes) - rarely, usually η^4

So.....

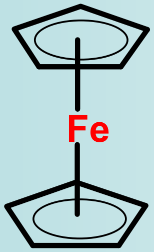
The number of electrons on the free metal

+ sum of the η number of the hydrocarbon ligands **+ sum of the electrons donated by other ligands**

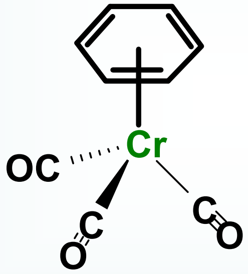
+ any negative charge on the complex **- positive charge on the complex**

Should = 18 normally

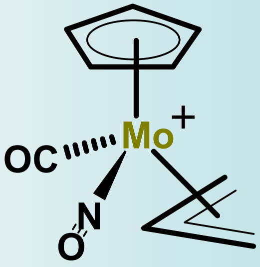
Many exceptions with early or late transition metals ; works best with middle transition metals



8 (Fe) + (2x5) = 18e$^-$

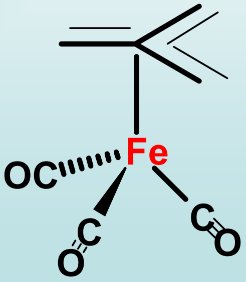


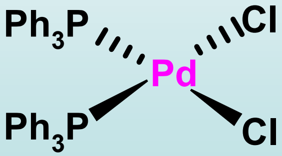
6 (Cr) + 6 (Ph) + (3x2) = 18 e$^-$



6 (Mo) + 5 (Cp) + 2 + 3 +3 -1 = 18 e$^-$

8 + 4 (TMM) + (3x2) = 18 e$^-$





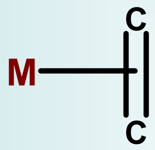
10 (Pd) + (2x2) + (2x1) = $\underline{16}$ e$^-$

Bonding of Hydrocarbon Ligands

- In its simplist form, bonding of the π- system to a transition metal fragment is based on the

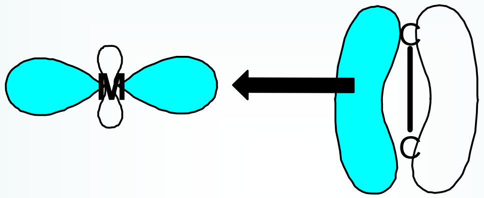
Dewar-Chatt-Duncanson Model

Consider



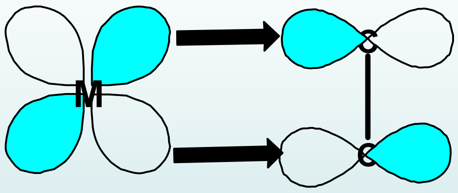
- There are two contributions to bonding

1) Ligand to Metal Donation



Note: this is not a π- bond, but rather a σ- bond

2) Metal to Ligand Back Donation



Note: this is a π- bond

Dewar, M. J. S. *Bull. Chim. Soc. Fr*. **1951**, C71.

Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939.

For higher level descriptions:

η^3, η^4, η^5 - see Yamamoto, A., p. 58-72

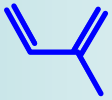
η^6 - see Collman, Hegedus, Norton, Finke p. 43-47

Consequences of Bonding of Hydrocarbon Ligands

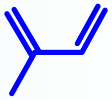
1) - In the alkene, the C=C bond is made <u>weaker</u> by complexation

2) - The ligand may be made more *or* less electron rich by complexation
-depends on case

3) - The organic fragment often loses its only plane of symmetry
-for example

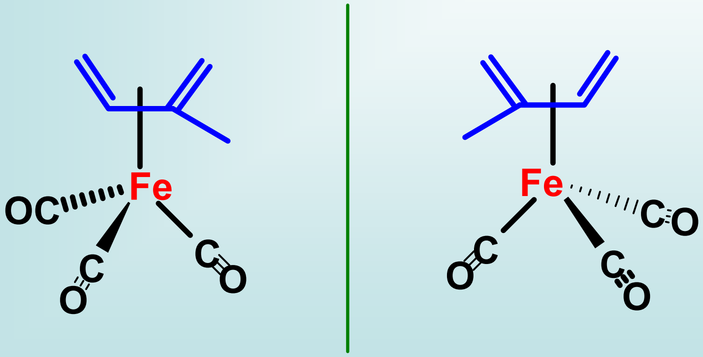


and



are the same compound

But.......

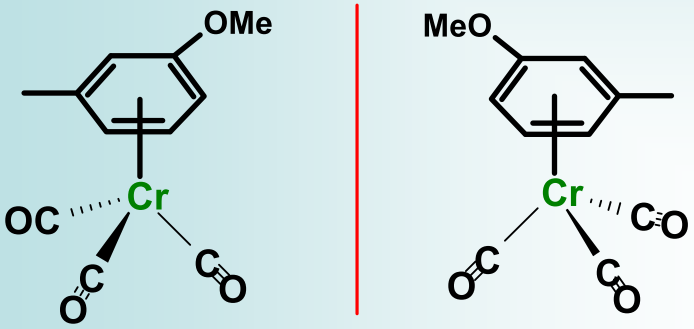


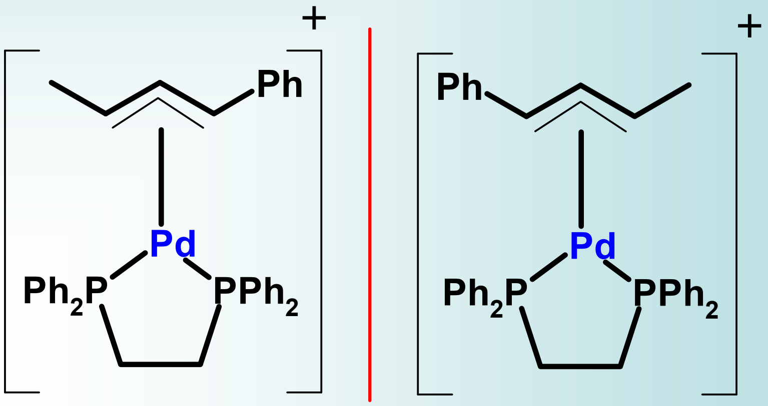
mirror image

These are not the same compound
- the plane of symmetry is destroyed

No non-superimposable mirror images
<u>Enantiomers</u>

Other examples





Same situation: Each pair is enantiomeric

Basic Organometallic Reactions

There are several additional fundamental types of reactions in organometallic chemistry

The more complex reactions are normally some combination of these fundamental ones

1) Lewis Acid Dissociation

- many transition metal compounds, especially hydrides, can lose as Lewis acid (i.e., deprotonate)

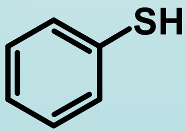
$$H{-}Co(CO)_4 \rightleftharpoons H^+ + {}^-Co(CO)_4$$

change in number of metal valence e$^-$'s	**0**
change in formal metal oxidation state	**-2**
change in coordination number at the metal	**-1**

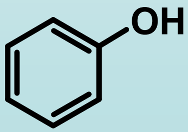
This may be a surprise, but many transition metal hydrides are quite acidic
-notice that making the metal more electron rich decreases acidity

$HCo(CO)_4$ **(pK_a = 8.3, CH_3CN)** $H_2Fe(CO)_4$ **(11.4)** $HCo(CO)_3PPh_3$ **(15.4)**

Winkler, J. R. et al (Gray, H. B.) *J. Am. Chem Soc.* **1986**, *108*, 2263.

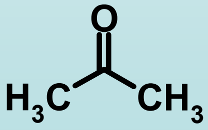


(pK_a = 10.3, $CH_3S(O)CH_3$)



(18.0)

H_2O **(32.0)**



(24.4)

2) Lewis Base Dissociation

Very, very, very..........common process

$$\overset{18e}{\mathrm{Fe(CO)_5}} \rightleftharpoons \overset{16e}{\mathrm{Fe(CO)_4}} + \mathrm{CO}$$

$$\overset{16e}{\mathrm{Pd(PPh_3)_4}} \rightleftharpoons \overset{14e}{\mathrm{Pd(PPh_3)_3}} + \mathrm{PPh_3}$$

change in number of metal valence e^-'s	**-2**
change in formal metal oxidation state	**0**
change in coordination number at the metal	**-1**

-Reverse reaction: Lewis base Association

Obvious application are in ligand substitution processes, which may be dissociative ('S_N1 like')

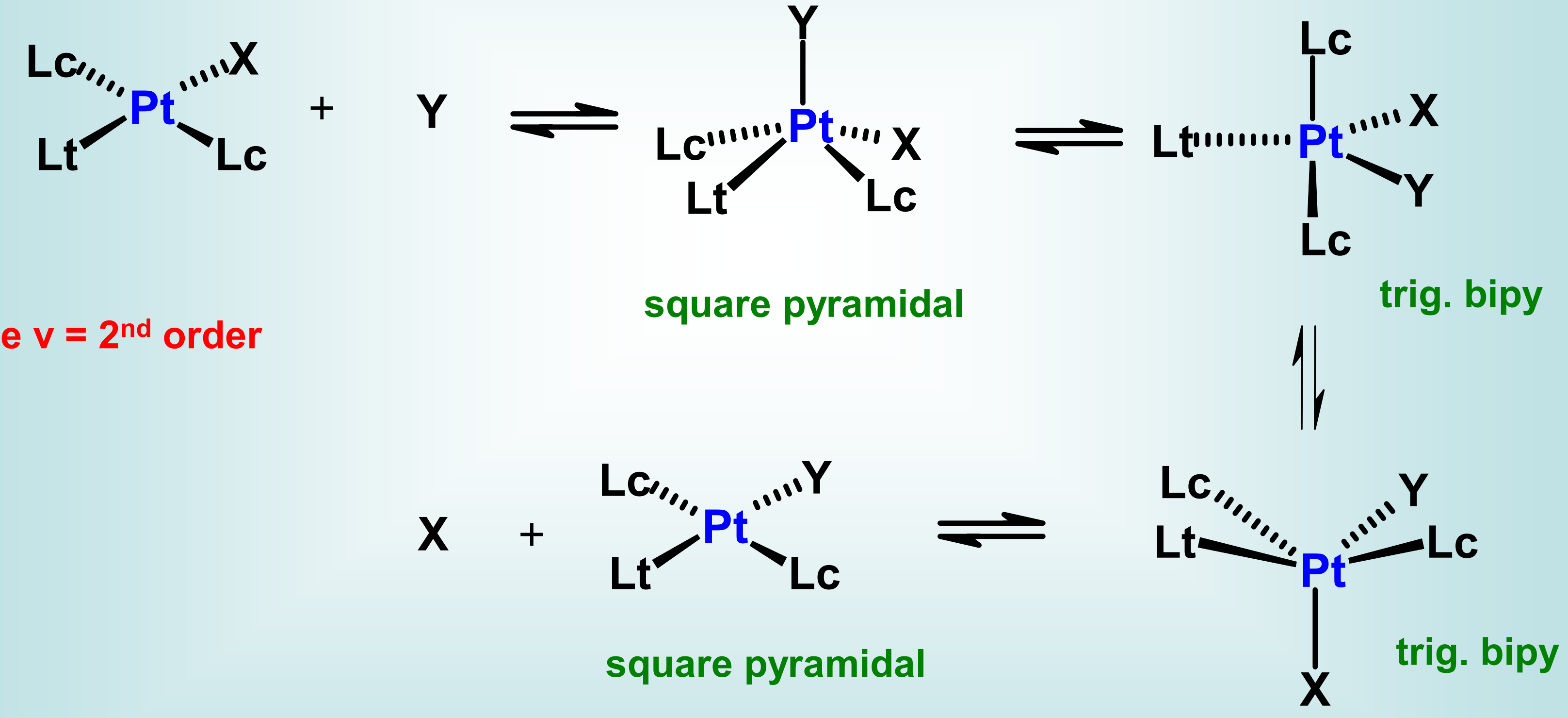
$$\mathrm{Ni(CO)_4} \overset{\text{slow}}{\rightleftharpoons} \mathrm{Ni(CO)_3} + \mathrm{CO} \xrightarrow[\text{fast}]{\mathrm{L}} \mathrm{LNi(CO)_3}$$

$v = k\,[\mathrm{Ni(CO)_4}]$ 1st order

Most common for 18 e^- systems

- Alternatively, this can be <u>associative</u>, i.e., "S_N2 like"

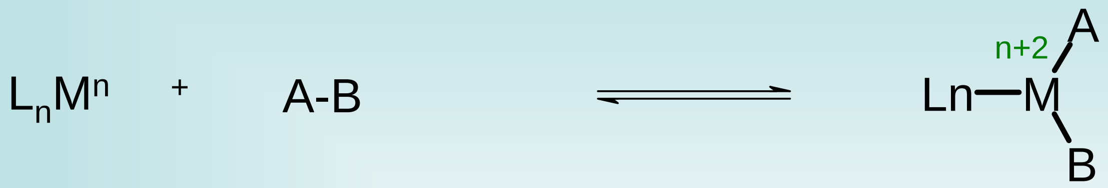
-more common fo 16 e^-, d^8 square planar complexes (i.e., Ni^{II}, Pd^{II}, Pt^{II} Rh^I, Ir^I)



rate v = 2nd order

3) Oxidative Addition

- represented by



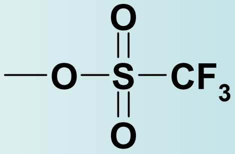
$$L_nM^n + A\text{-}B \rightleftharpoons L_nM^{n+2}(A)(B)$$

change in number of metal valence e$^-$'s	**+2**	**(14 - 16 e)**
change in formal metal oxidation state	**-+2**	**(0 - +2)**
change in coordination number at the metal	**+2**	

for more details, see: R Yamamoto pp. 222-239
R Collman & Hegedus pp. 279-321

-Overall reaction is cleavage of the A-B bond with bonding to the metal

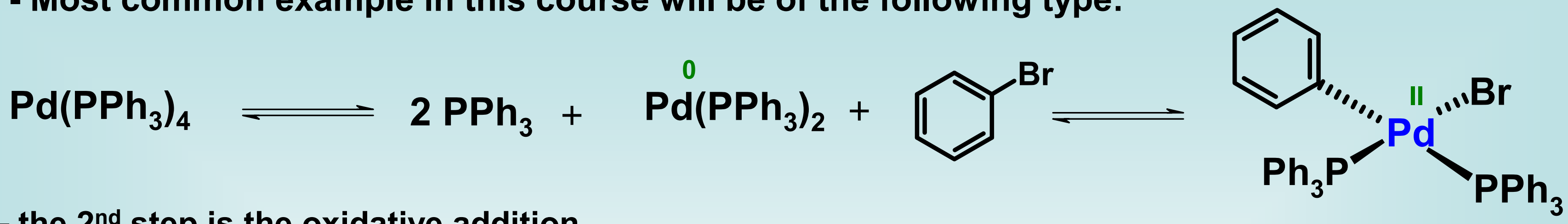
- Most common A-B is R_3C-X X = halogen or pseudohalogen



triflate

-Classic 'organic' example is Grignard reagent formation

- Most common example in this course will be of the following type:



- the 2nd step is the oxidative addition

Therefore, system needs: a) 2 available oxidation states i.e., Pd^{o}/Pd^{II} , Fe^{o}/Fe^{II}, Ir^{I}/Ir^{III}

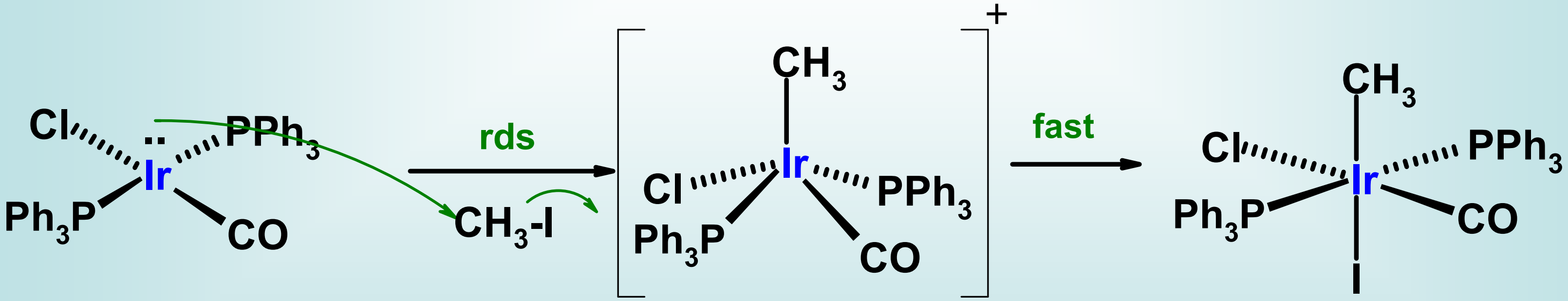
b) open coordination site

- Reverse reaction: Reductive Elimination

Mechanism

- Most is known about late transition metals (such as Ir, Ni groups)

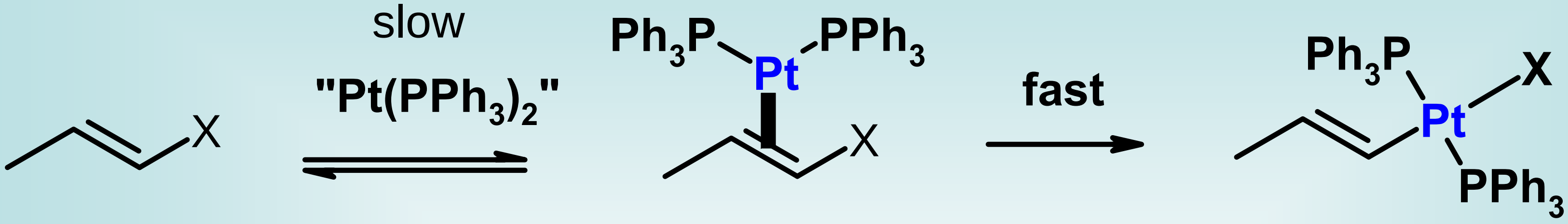
A) If the R of R-X is alkyl (especially 1° or 2°), the reaction is believed to (usually) occur via an S_N2 substitution



- *Inversion* at alkyl carbon *has* been observed

- Kinetics are overall 2nd order $v = k\,[Ir^{I}]\,[CH_3I]$

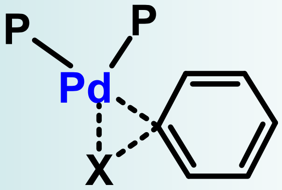
B) Vinyl (and perhaps aryl) halides go via π - complex formation, with ultimate direct insertion

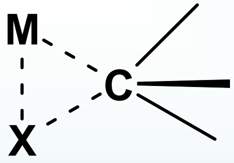


- Goes with retention of configuration of C=C configuration
- Also believed to be mechanism for addition of H_2

B') Aryl halides go via direct insertion into C-X bond (*clearly related to B*)

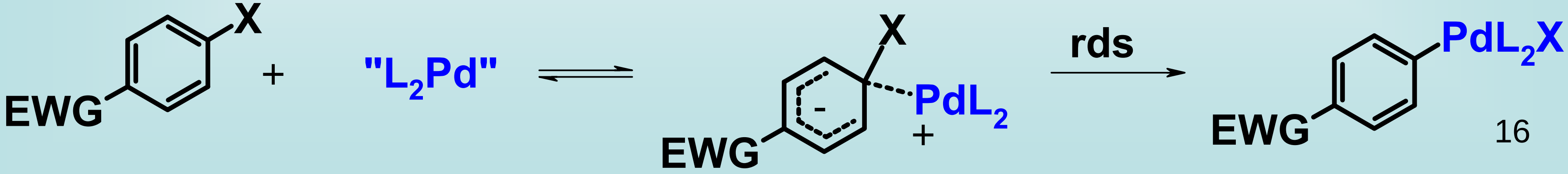
i.e.,



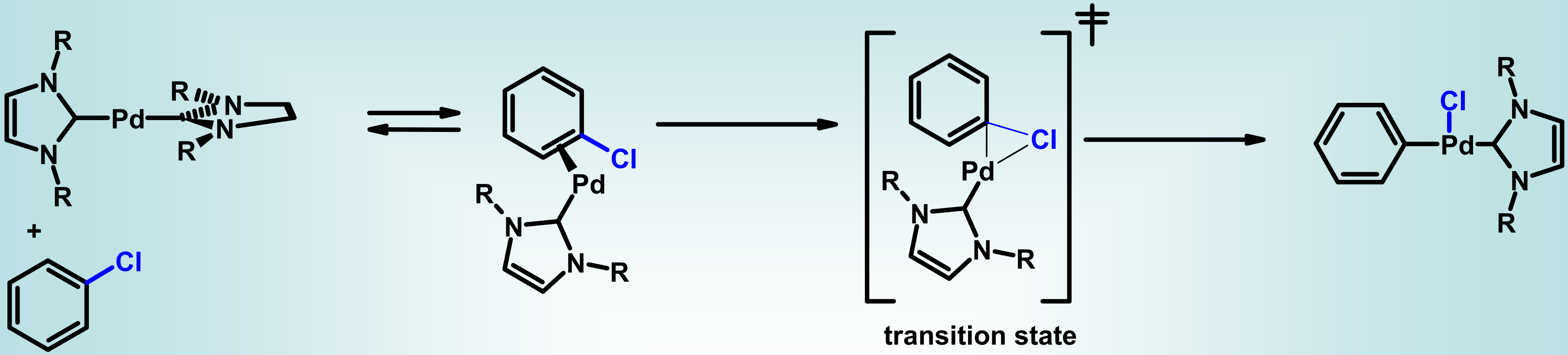


Could result in retention of configuration in some cases

C) - Now defrocked - Nucleophilic Aromatic Substiution - was an old proposal for aryl cases, to rationalized that <u>cases with electron withdrawing groups "always" go *faster*</u>



C)' - much more likely and often detected in calculations is initial formation of an η^2-benzene complex

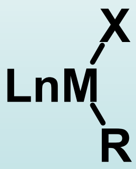


Green, J. C. J. Organomet. Chem. **2005**, *690*, 6054.

D) - Electron transfer, radical mechanisms do exist (Ni, Mg)

i.e. $L_n + RX \xrightarrow{\text{rds}} [\,L_nM^+ \quad RX^{-\cdot}]$

$[\,L_nM^+ \quad RX^{-\cdot}] \longrightarrow$



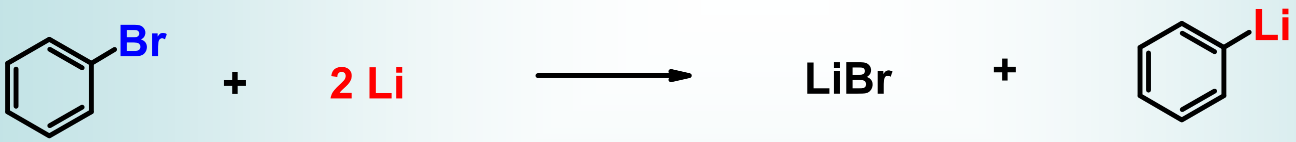
$$L_nM(X)(R)$$

Bi, S. *Chem. Phys. Lett.* ***2006,*** *431*, 385.

Aside: One electron oxidative additions also exist

$$2\ L_nM^{o} \quad + \quad A\text{-}B \longrightarrow L_n\overset{I}{M}\text{-}A \quad + \quad L_n\overset{I}{M}\text{-}B$$

Conventional organic example - Lithium-Halogen exchange

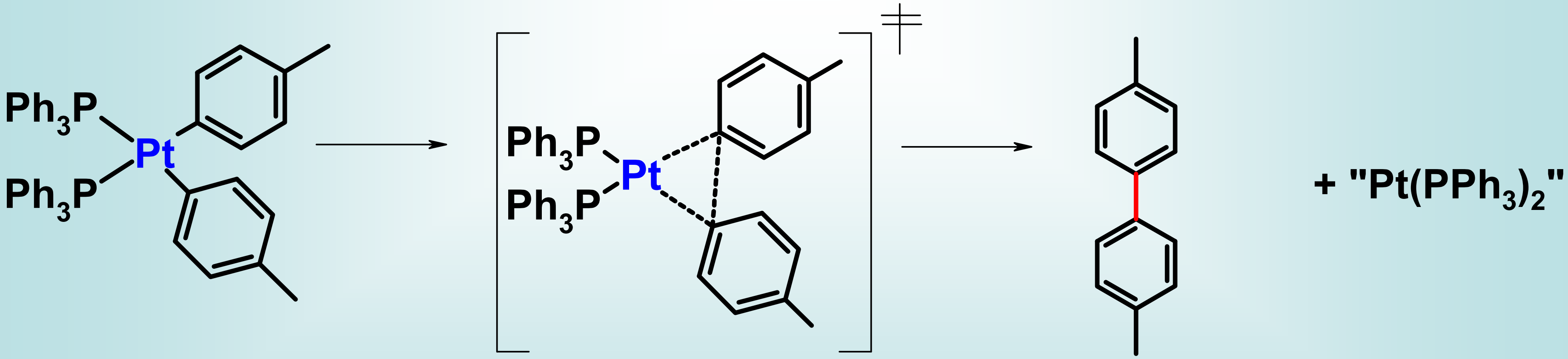


Many new opinions on these matters:

R Hartwig, J. F. Synlett **2006**, 1283.
R Espinet, P.; Echavarren, A. M. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 4704.
R Jutand, A. *Eur. J. Inorg. Chem.* **2003**, 2017.
Alcazar-Roman, L. M.; Luis, M.; Hartwig, J.F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618. (chelate PR$_3$)
Hartwig, J. F.; Paul, P. *J. Am. Chem. Soc.* **1995**, *117*, 5373 (monodentate PR$_3$)
R Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.
Lersh,M.; Tilset, M. *J. Am. Chem. Soc.* **2005**, *127*, 2471 (C-H activation).

4) Reductive Elimination - reverse of oxidative addition

change in number of metal valence e⁻'s	-2	(16e - 14e)
change in formal metal oxidation state	-2	(+2 - 0)
change in coordination number at the metal	-2	



transition state
-not an intermediate

In 'normal' cases, the reaction goes by a concerted mechanism

-and, importantly for organic chemists.......

<u>retention</u> of configuration
at carbon

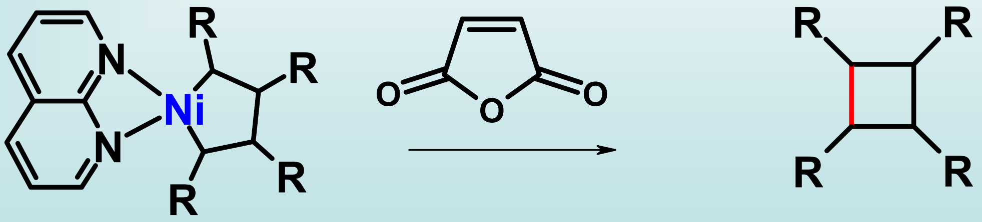
Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981

Note: Whether the precursor is square planar or trigonal bipyramidal, it's the *cis* groups which reductively eliminate

Other notes on reductive elimination:

- **Again, need two accessible oxidation states**
- **Non 18 e^- situations must be accessible**
- **Ni group (Ni, Pd, Pt) are the usual synthetic choices**

Since metal becomes more electron rich during the reaction, the reaction is sometimes accelerated by addition of a ligand which is electron withdrawing



More details in general:

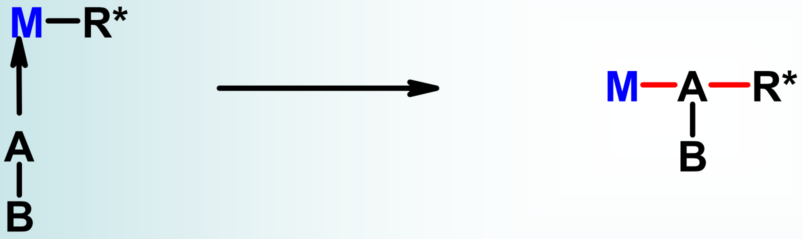
Yamamoto, pp. 240-5
Collman, Hegedus pp 322-33

5) Insertion (Migration)

-There is more than one type possible

M-R is a
Metal-C or
Metal-H bond

or

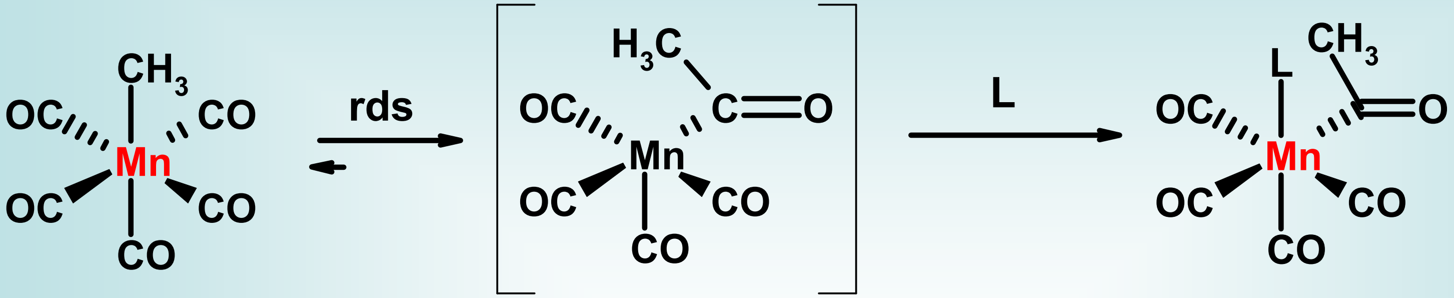


A=B is $R'_2C{=}CR'_2$ $R'_2C{=}O$ $R'_2C{=}NR'$

:A—B is $:C{=}O$ $:C{=}NR'$ $:CR'_2$

Most common :A-B is CO

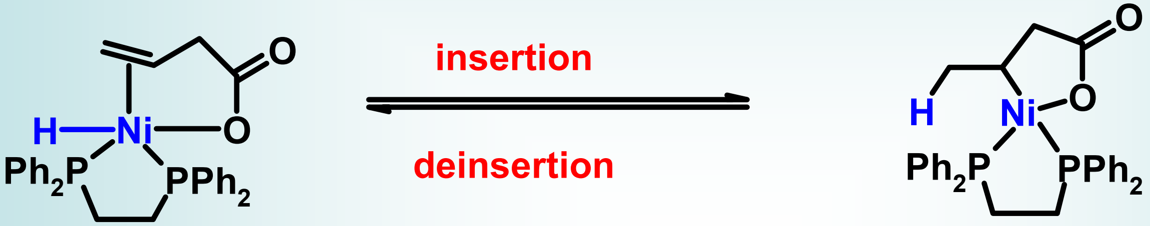
-The reaction is a concerted migration of R*, with retention of configuration at R* and the metal, if they are chiral



Change in # of valence electron at the metal	-2	(18 to 16e)
Change in metal oxidation state	0	(+1 to +1)
Change in coordination number	-1	(6 to 5)

Note: Reverse reaction is <u>deinsertion</u>

Most common A=B in this case are alkenes or alkynes
-for example, the intermediate step in hydrogenation



- The reverse reaction in this case (β-elimination) is one of the most common reactions of alkylmetals - main mode of decomposition

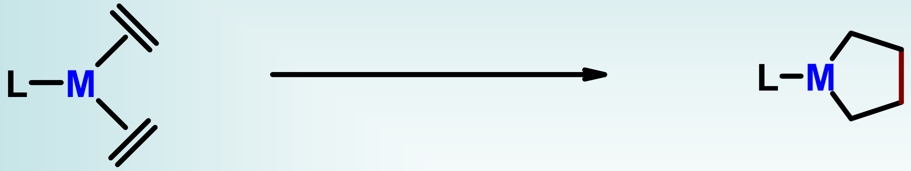
-again, if inserting group is alkyl, generally there is <u>retention</u> of configuration at R*

see <u>R</u> Cross, R. J., in "Chemistry of the Metal-Carbon Bond", Hartley and Patai, 1982, V.2

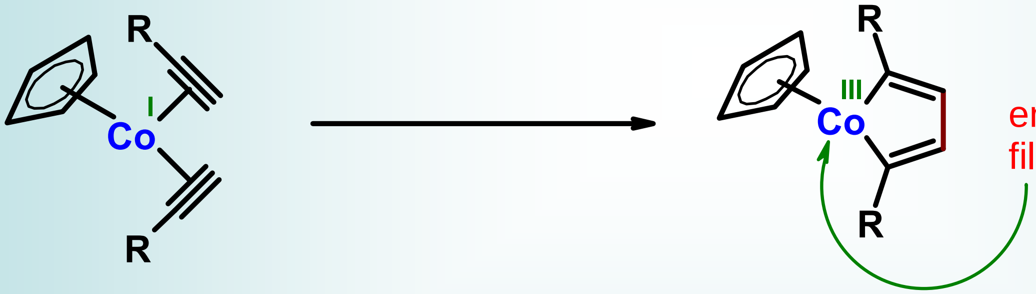
<u>R</u> Yamamoto, p. 246-272

6) Oxidative Coupling

Oxidative coupling occurs when two 'π-bound' ligands on the metal react with each other to form (usually) a C-C σ bond



One of the best known examples is....



empty coordination site ultimately filled by a ligand

-This has become increasingly important with a variety of metals and transformations

Change in number of valence electrons at metal	**-2 (18 to 16e)**
Change in metal oxidation state	**+2 (+1 to +3)**
Change in metal coordination number	**0 ('3' to '3')**

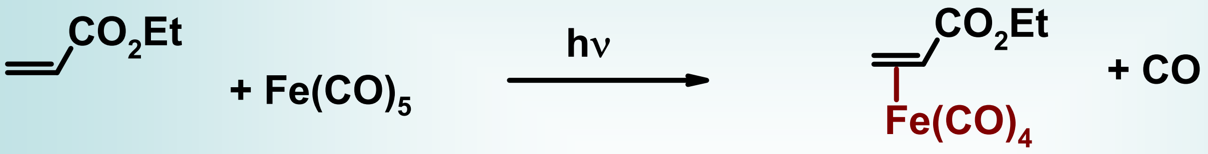
Note: There are several other fundamental mechanisms, but they have a close 'organic' analogy

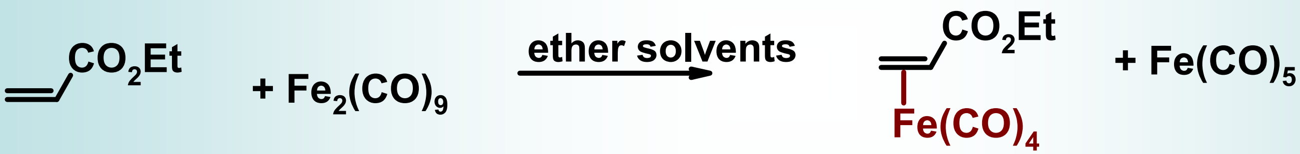
η^2-Olefin/Acetylene Complexes

a) Preparation

i) -most common method - ligand exchange (with CO, CH_3CN, alkenes)

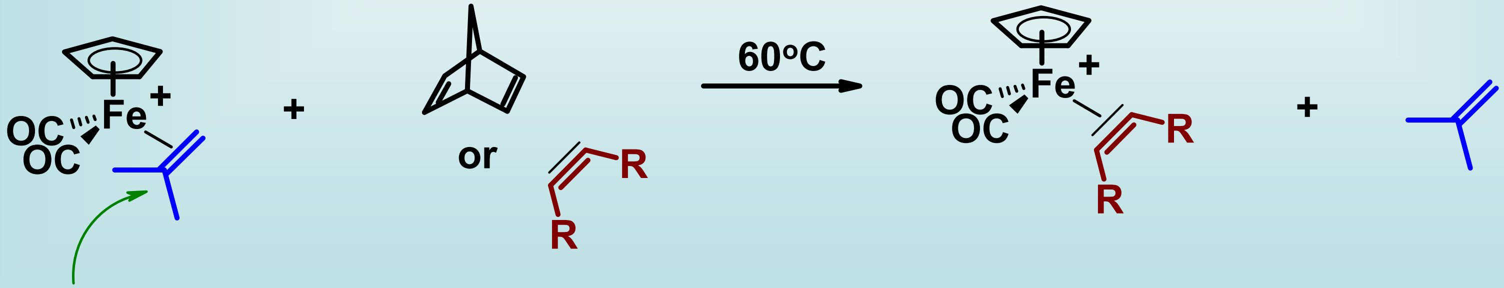
i.e., with Fe° it is almost always as follows





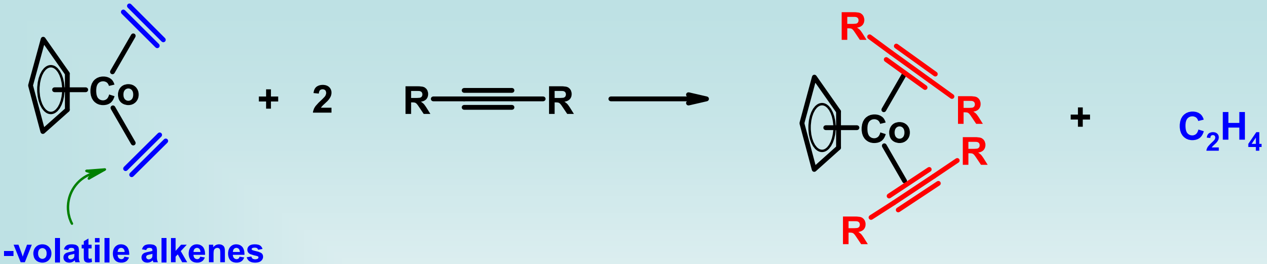
Weiss et al *Helv. Chim. Acta*. **1963**, *46*, 288

Note: The departing ligand doesn't need to be CO - some other examples

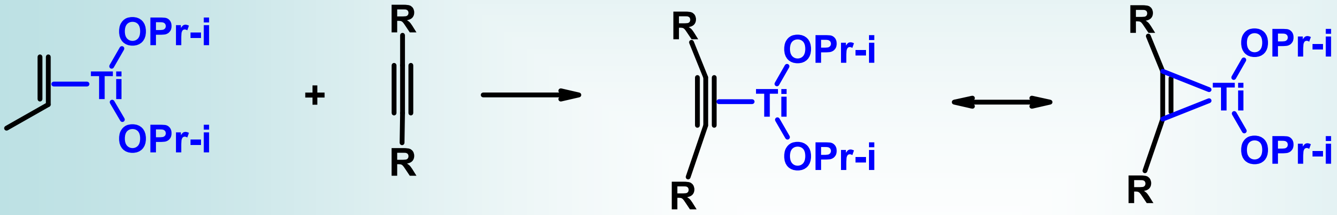


-sterically hindered alkene

Cutler, M. et al (M. Rosenblum) *J. Am. Chem. Soc.* **1976**, *98*, 3495



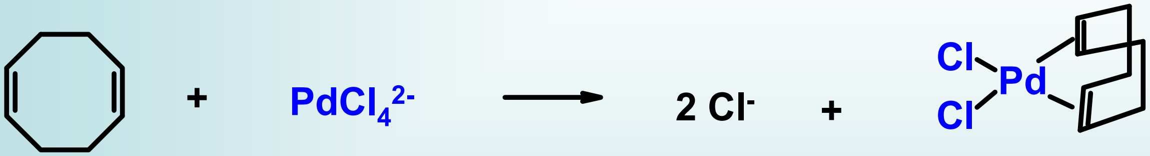
Jonas, K. et al *Angew. Chem. Int. Ed. Engl.* 1983, *22*, 716.

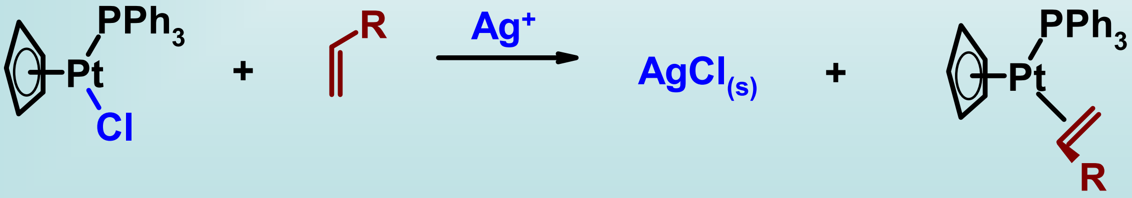


R Sato, F.; Okamoto, S. *Adv. Synth. Catal.* 2001, *343*, 759.

ii) Synthesis by Displacement of Halide

Cl^- may be displaced by an alkene, either on its own or with an assisting Lewis acid (S_N1 like reactivity)

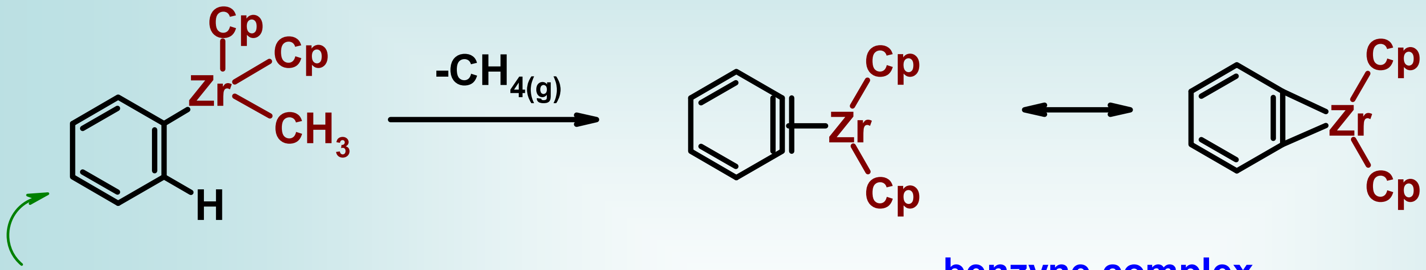




Schultz, R. G. *J. Organomet. Chem.* 1966, *8*, 435
Davies, S. G. et al *J. Organomet. Chem.* 1986, *188,* C41.

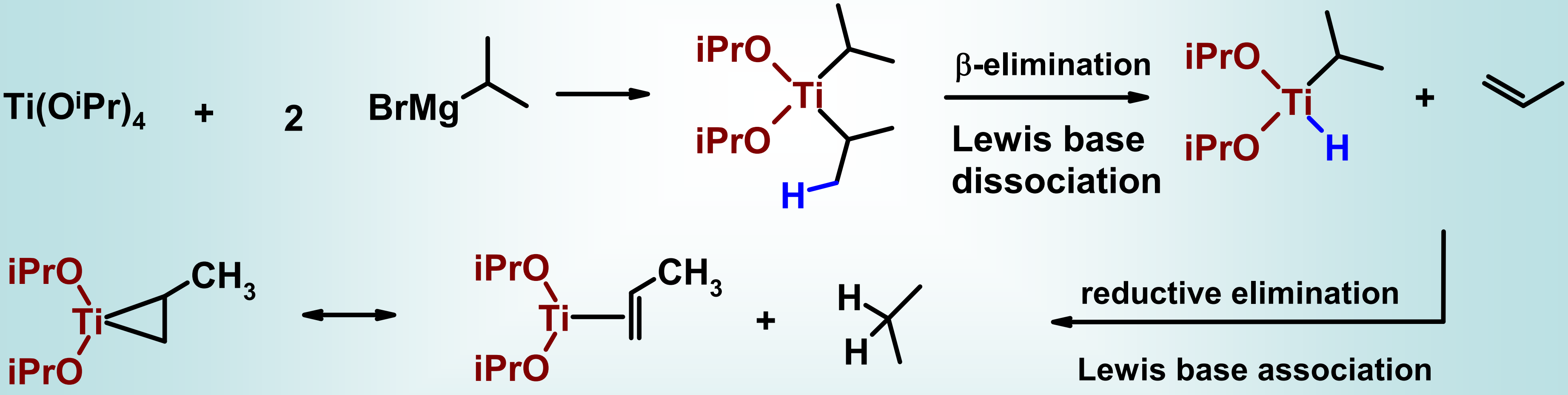
iii) -by hydride abstraction (also called σ-bond metathesis)

- this type is common for the preparation of alkene and alkyne early transition metal complexes



accessible from the organolithium

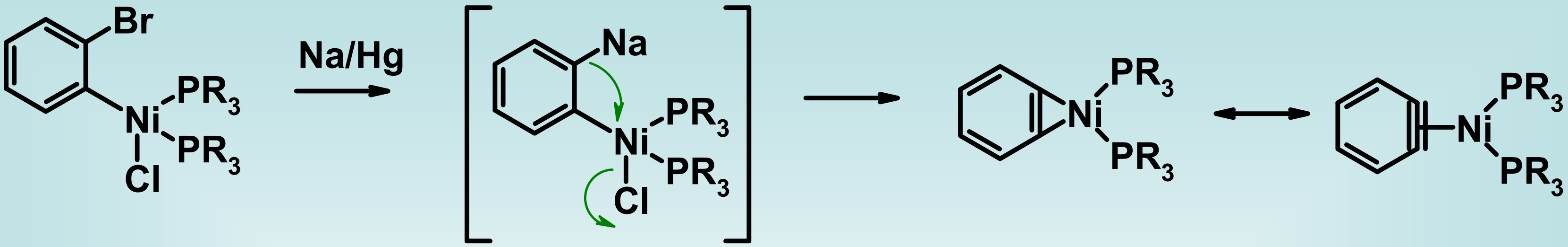
benzyne complex



Buchwald, S.L.; Nielsen, R. B. *Chem. Rev.* 1988, *88*, 1047.
see also Sato review

iv) - By intramolecular nucleophilic substitution

-often for alkyne complexes, with a wider variey of metals than hydride abstraction

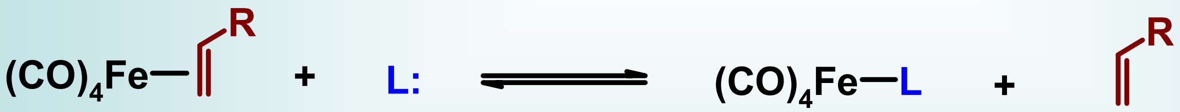


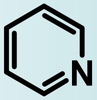
R Bennett, M. A. *Chem. Ber./Receuil* 1997, *130*, 1029.
R Bennett, M. A. *Pure Appl. Chem.* 1989, *61*, 1695.
R Bennett, M. A. *Angew. Chem. Int. Ed. Engl.* 1989, *28*, 1296.

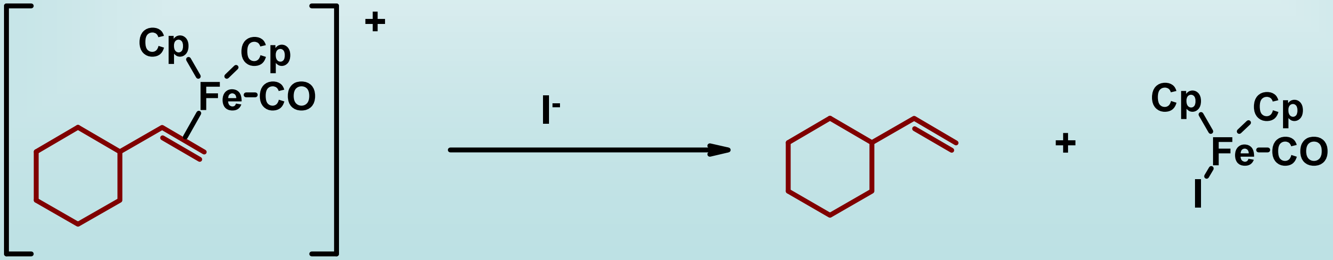
b) Getting Rid of Them (Decomplexation)

-most organic chemists want the metal removed from the organic 'ligand' at the end of the process

i) Competitive ligand association



most common L include another alkene or alkyne, R_3P, CO, 



ii) oxidation of the metal

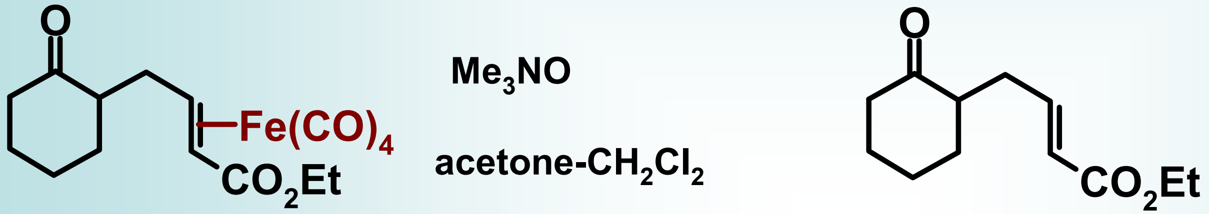
-very often, if one oxidizes the metal, it no longer bond very well to the organic ligand, and it simply falls off

-several very common oxidants include.....

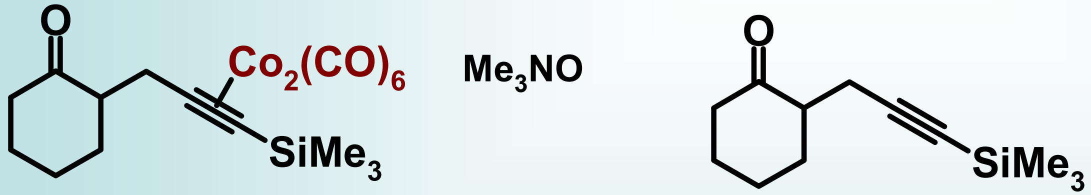
$FeCl_3$, Ce^{+4} ($(H_4N)_2Ce(NO_3)_6$), others

Me_3N^+-O^- (trimethylamine N-oxide, N-methylmorpholine N-oxide)

Shvo, Y.; Hazum, E. *J. Chem. Soc., Chem. Commun.* 1974, 336 (for iron diene compelxes)



Green, J. R.; Carroll, M. K. *Tetrahedron Lett.* 1991, *32*, 1141.



R Nicholas, K. M. *Acc. Chem. Res.* 1987, *20*, 207.

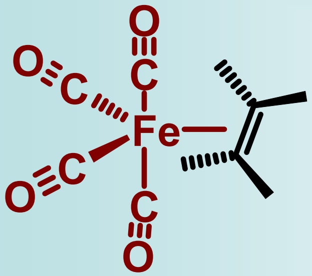
c) Uses of η^2- Metal Complexes

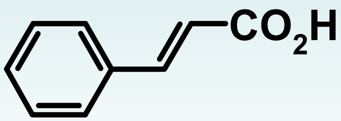
i) as a protecting group

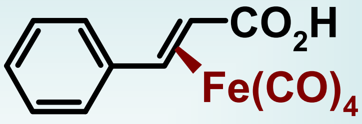
-recall the intro.....that olefin coordination changes the electron density of that alkene

-can make the alkene more *or* less reactive than the uncomplexes alkene, depending upon the case

Consider......

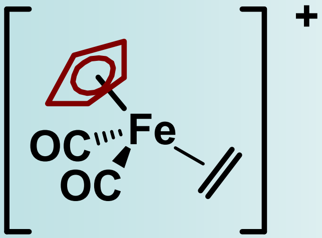






-therefore, ***very*** slightly overall electron donating (essentially the same)

but

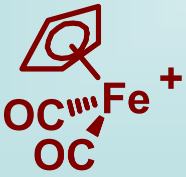


charge on complex almost unboubtedly renders η^2-complex <u>less</u> electron rich

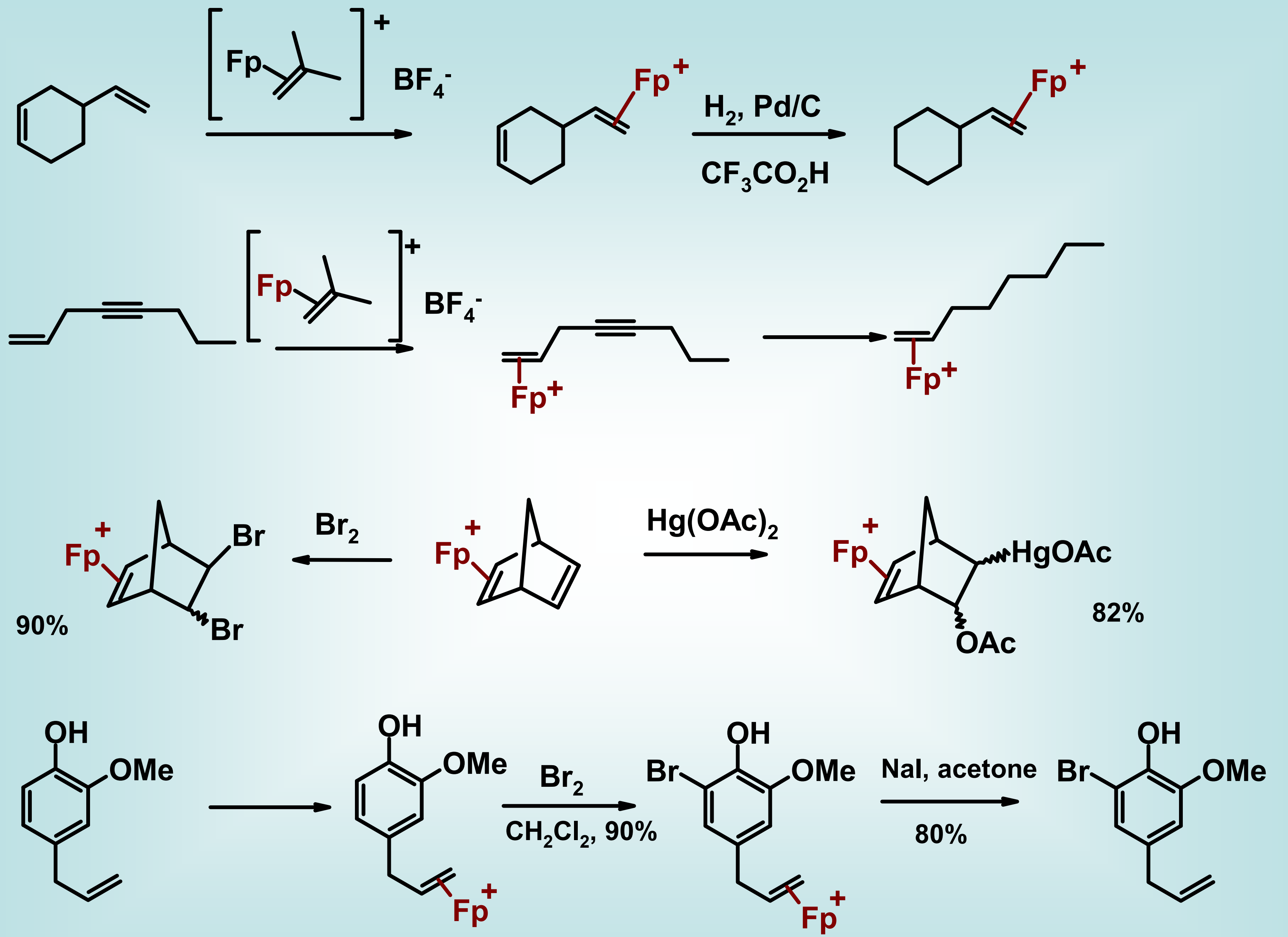
-as a result, the alkene is less reactive to attack by E^+, and to hydrogenation

-but(!), the alkene is more reative to attack by Nu^-

Note:



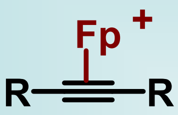
= Fp^+

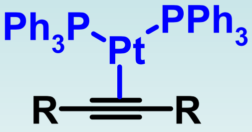


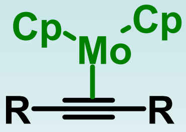
-Fp^+ alkene complexes are air stable, water stable, and you can store them at 0°C

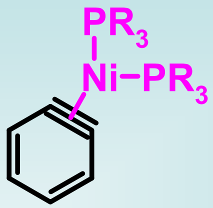
Alkynes

-many alkyne complexes known

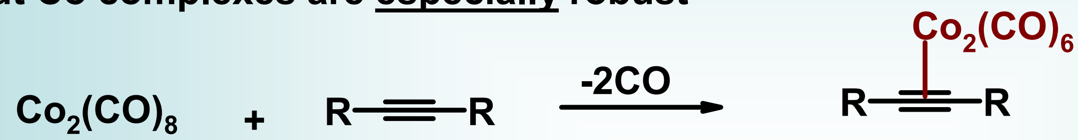




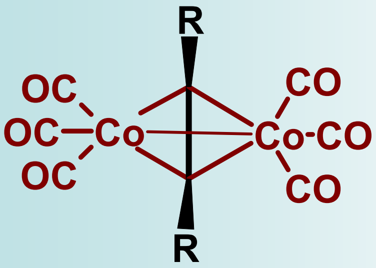




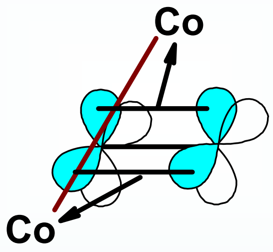
But Co complexes are <u>especially</u> robust



not real structure, of course



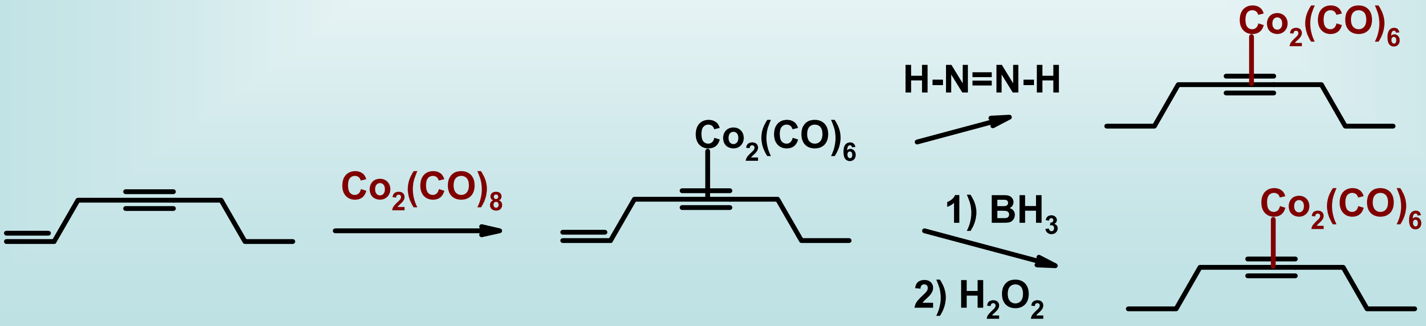
or



-bonding is called $\mu-\eta^2$ $(\mu^2\text{-}\eta^2)$

-these are in general very stable complexes

-since p- bonds are used in bonding to metals as well, they are not available to electrophiles, like most other alkynes are



<u>R</u> Nicholas, K. M. *Acc. Chem. Res.* <u>1987</u>, *20*, 207.

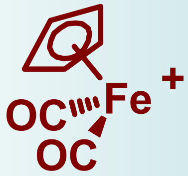
η^2-Complexes as Electrophiles

a) Cationic Complexes (Fp$^+$)

-just as the '+' charge, nominally on Fe, ultimately withdraws electron density from the alkene and reduces its reactivity to electrophiles (E$^+$)....

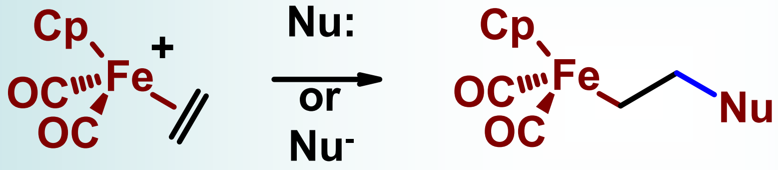
-so it by contrast increased reactivity of alkenes to nucleophiles (Nu$^-$)

The stoichiometric chemistry is dominated by chemistry of



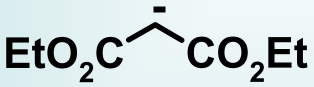
= Fp$^+$

Thus,

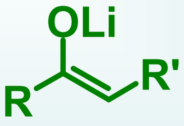


-list of Nu$^-$'s hat do this is pretty large

Carbon based



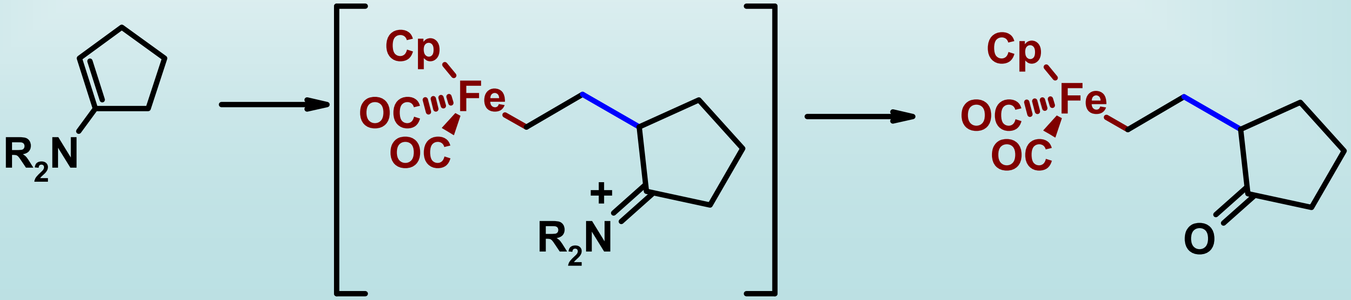
R_2CuLi



or

in some cases

enamines

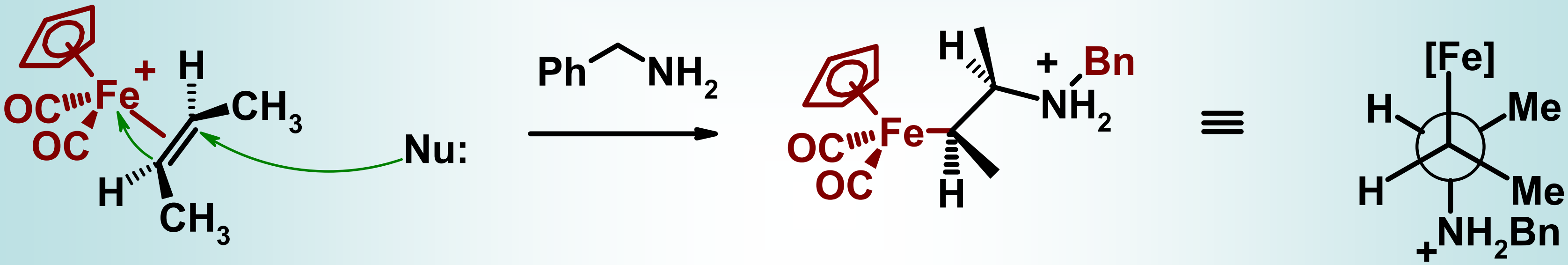


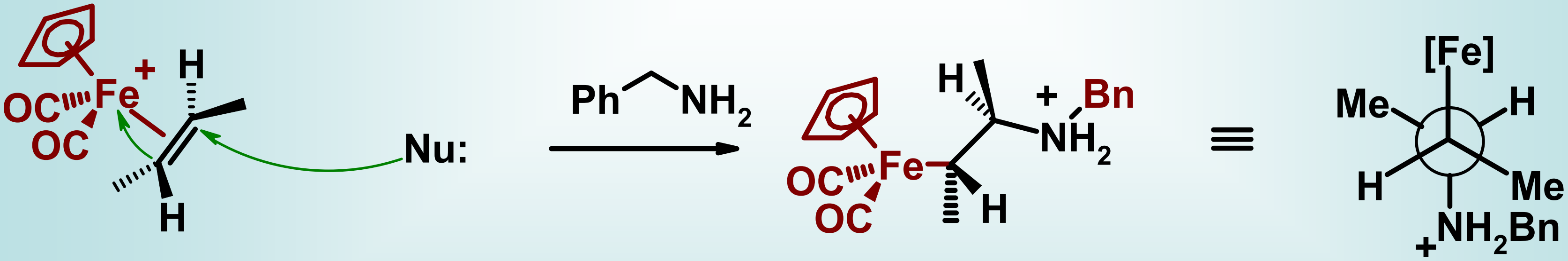
Heteroatom based

R_nNH_{3-n} ;	ROH (+Na_2CO_3);	RSH (+Na_2CO_3);	R_3P
(amines)	(alcohols)	(thiols)	(phosphines)

Stereochemistry of Addition

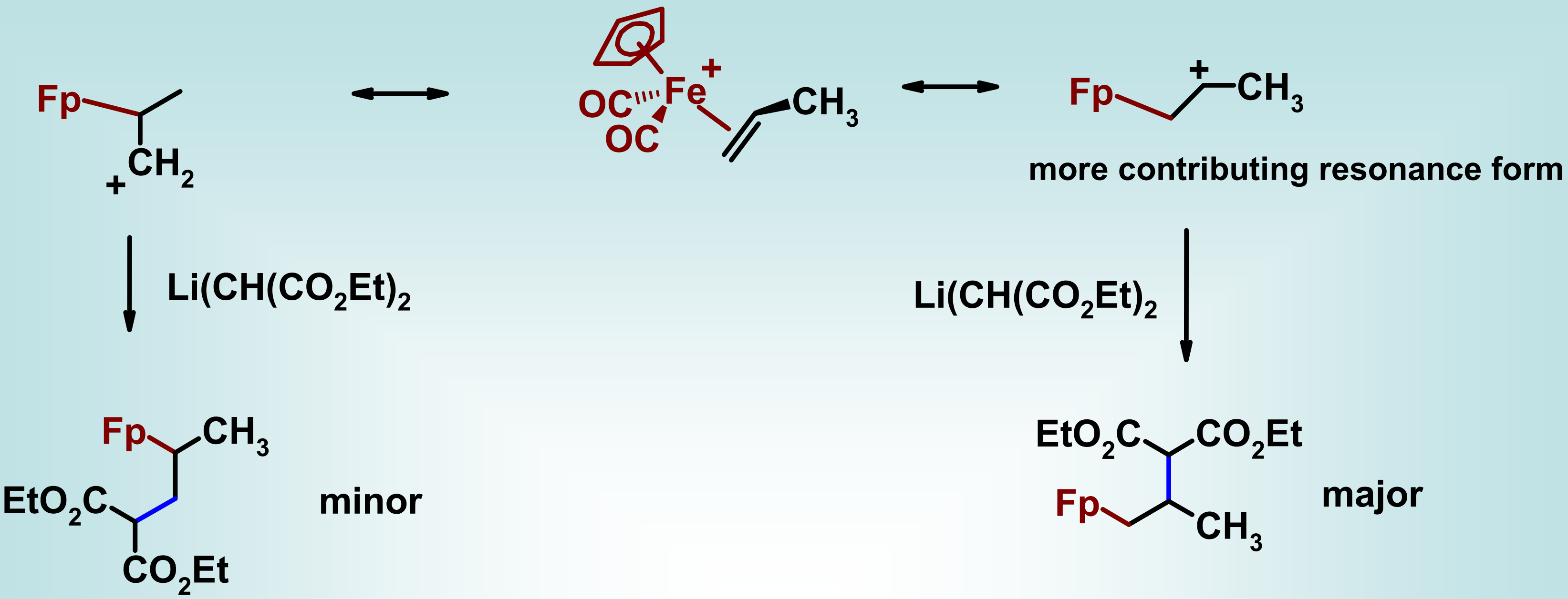
-The addition of Nu: or Nu^- is stereospecifically ***trans*** to the metal. So.....





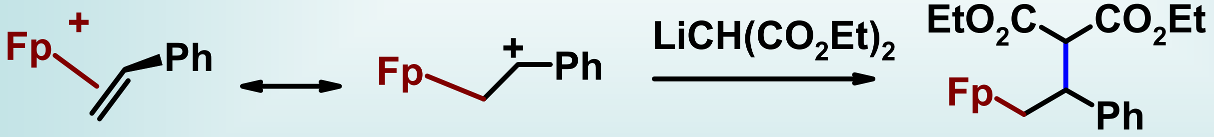
Regiochemistry

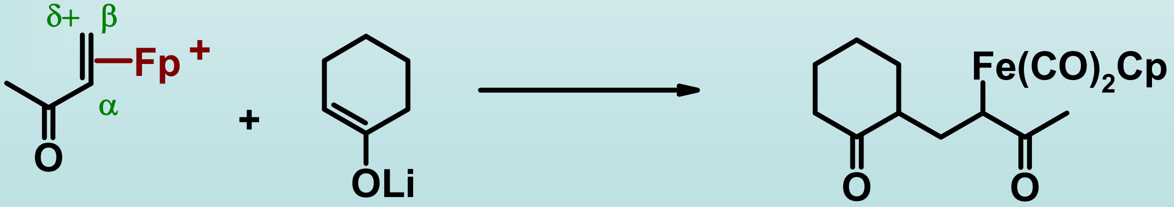
If you draw various resonance forms of the Fp^+-alkene cation complex, the nucleophile ends up attacking the carbon atom where the 'traditional' organic cation would be most highly stabilized (i.e., 'S_N1 like') reactivity



Note: Unfortunately, with simple alkyl substutuents (like above), the regioselectivity is pretty poor.

However, with strong cation stabilizing or detsabilizing (electron withdrawing) groups, the outcome is much more decisive





So what do you do with the products?

-there are very few natural products with covalent Fe-C bonds in them, so it's generally desired to turn these into something 'all organic'

1) -the alkyl-Fp compounds may be transformed into several functional groups, i.e....

$$\mathrm{Fp{-}R} \xrightarrow{\mathrm{I_2}} \mathrm{R{-}I} \qquad\qquad \mathrm{Fp{-}R} \xrightarrow[\mathrm{CS_2}]{\mathrm{Br_2}} \mathrm{R{-}Br}$$

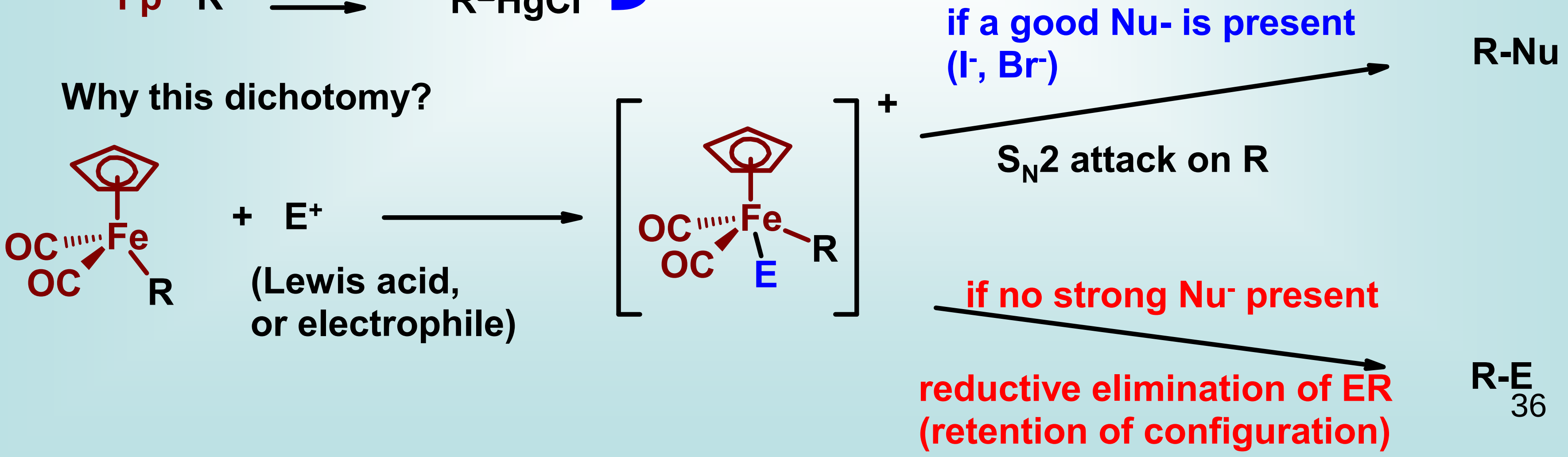
-normally, this occurs with ***inversion*** of configuration at the carbon being attacked.

But......

$$\left.\begin{array}{l} \mathrm{Fp{-}R} \xrightarrow[\mathrm{CF_3CO_2H}]{\mathrm{HCl\ \ or}} \mathrm{R{-}H} \\ \mathrm{Fp{-}R} \xrightarrow{\mathrm{HgCl_2}} \mathrm{R{-}HgCl} \end{array}\right\}$$

with ***retention*** of configuration at the carbon attacked!

Why this dichotomy?

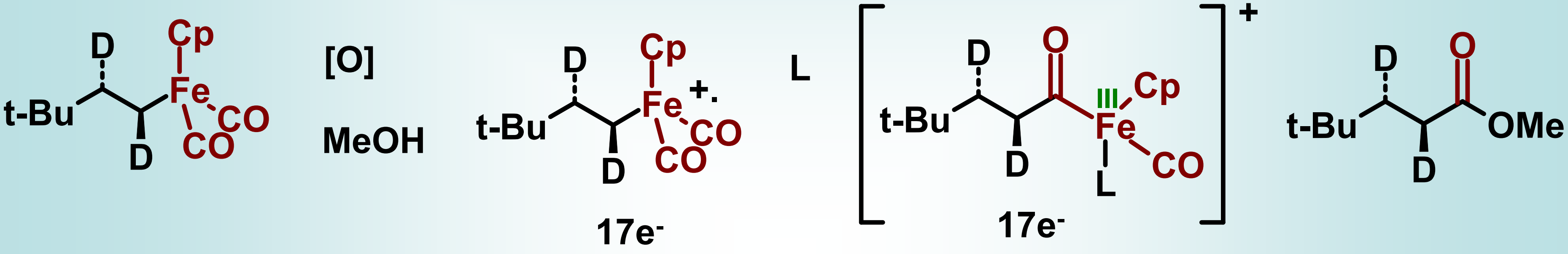


2) Oxidation

In the presence of an oxidant, migratory insertion of CO occurs before the metal is lost. The 17 e^- species does this very rapidly

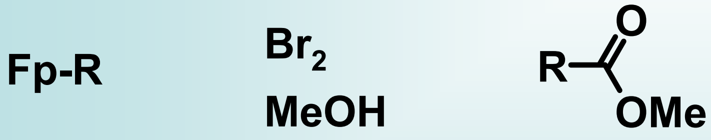
-common oxidants are Ce^{IV}, Fe^{III}, Cu^{II}, O_2

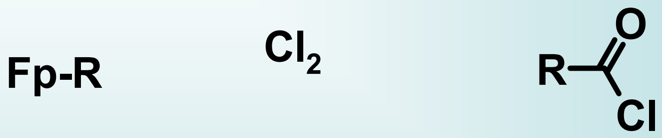
This is most often done in methanol solvent, so that the final product is a methyl ester.



notice the retention of configuration

This includes Br_2 and Cl_2 as oxidants

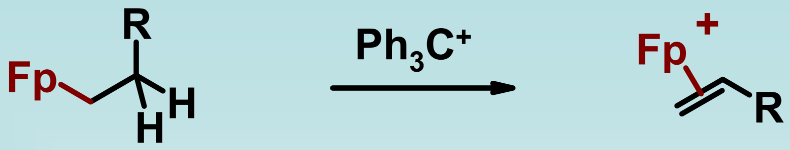




notice difference when solvent is CS_2

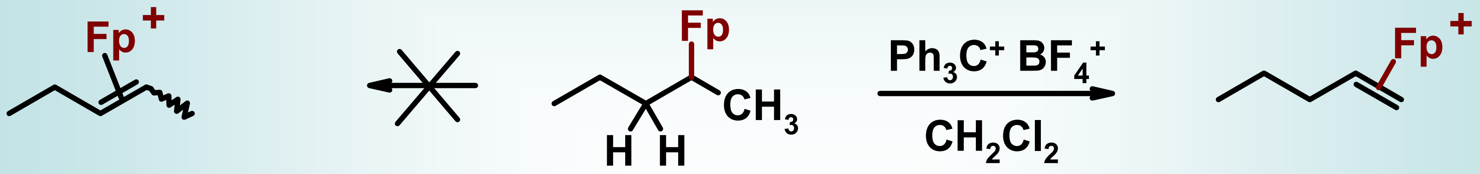
3) Elimination

If the is a H atom b- to the iron, which can assume an antiperiplanar conformation, it can be abstracted as H^-, usually by Ph_3C^+



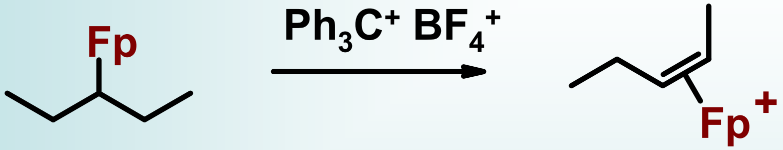
Rules for abstraction:

-if there is a choice between forming a terminal alkene and an internal one, one normally gets the *terminal* alkene - probably a steric accessibility argument



-if internal alkenes must be made, one gets mostly the (Z)- isomer

-no one really knows why....perhaps a greater stability of the complex



major

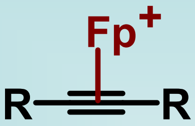
References:

R Pearson, A. J. 'Iron Compounds in Organic Synthesis', 1994, Ch.2
R Rosenblum, M. *J. Organomet. Chem.* 1986, *300*, 191.
R Rosenblum, M. *Pure Appl. Chem.* 1984, *56*, 129.
R Rosenblum, M. *Acc. Chem. Res.* 1974, *7*, 122.
R Green, J.R.; Donaldson, W. A. in 'Encyclopedia of Inorganic Chemistry' 1994, V. 2, p.1735.

Enantiomerically pure versions

Turnbull, M. M.; Foxman, B.M.; Rosenblum, M. *Organometallics* 1988, *7*, 200.
Begum, M. K. et al (Rosenblum) *J. Am. Chem. Soc.* 1989, *111*, 5252.

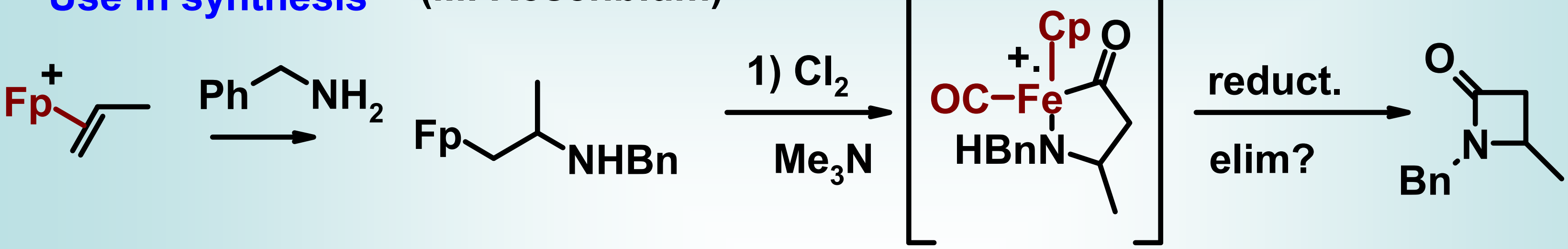
-some similar chemistry is known for the corresponding alkyne complexes, i.e.,

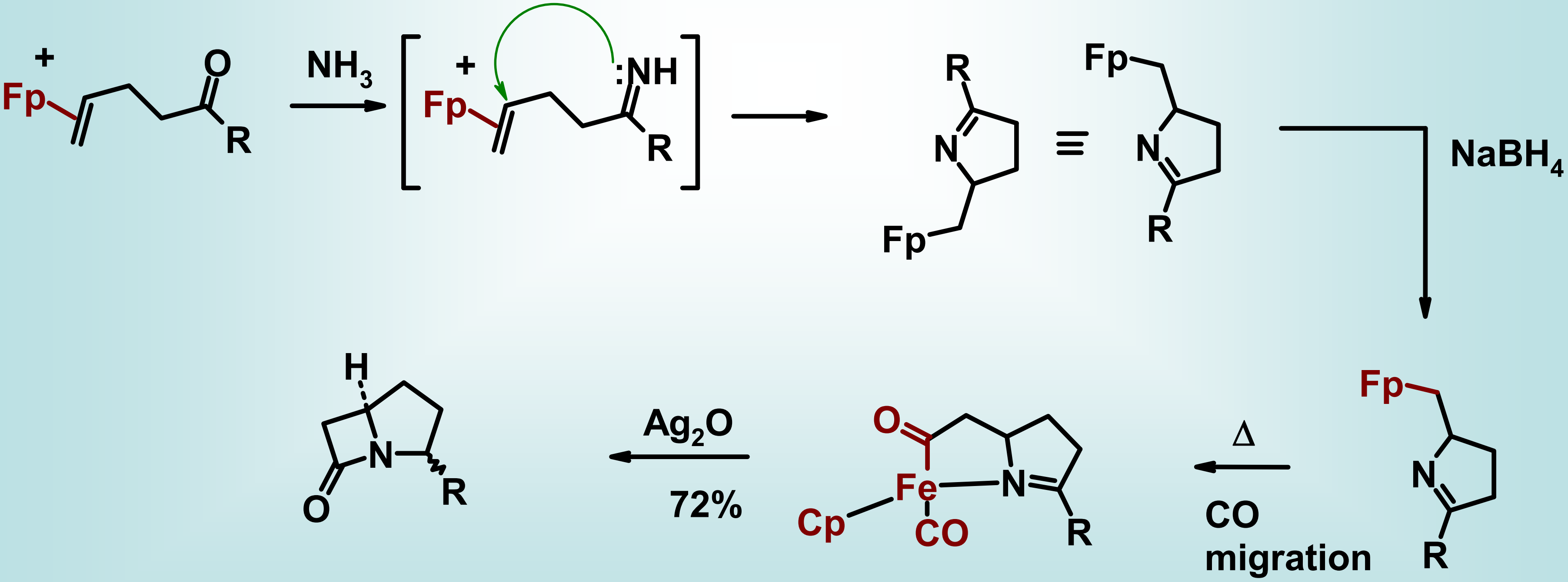


It is not nearly as well explored

see Reger, D.L. *Organometallics* 1984, *3*, 135 & 1759.

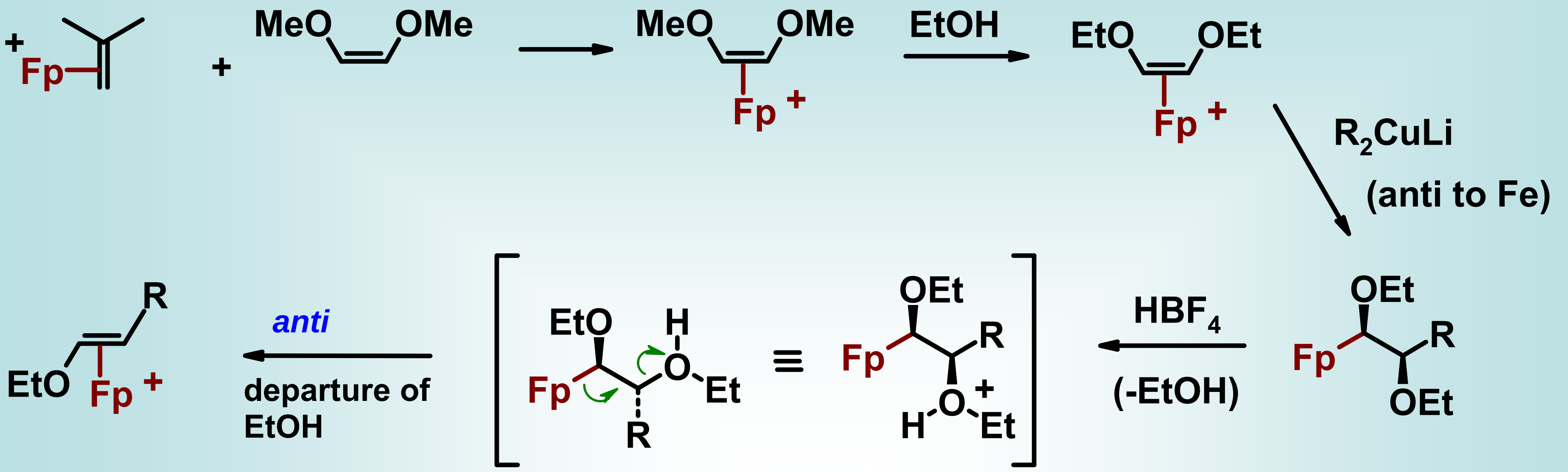
Use in synthesis (M. Rosenblum)



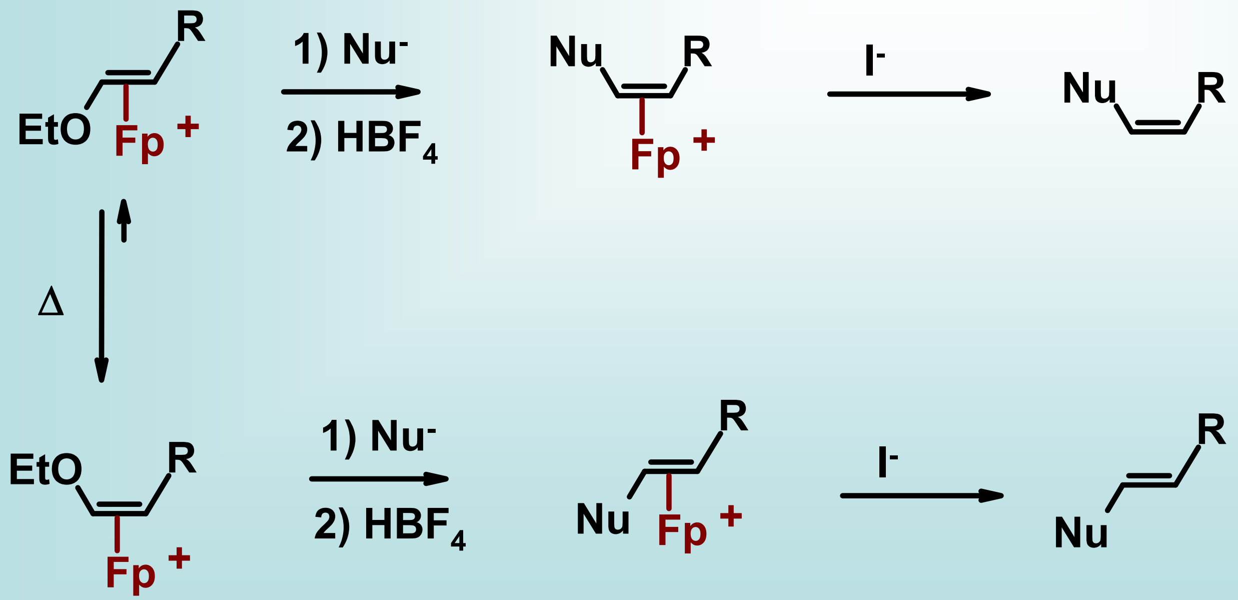


Wong, P. K. (Rosenblum) *J. Am. Chem. Soc.* 1977, *99*, 2823.
Berryhill, S. R. (Rosenblum) *J. Org. Chem.* 1980, *45*, 1984; 1983, *48*, 158.

Synthesis of stereochemically defined alkenes from enol ethers



This can be repeated, using other ether function, with modification to get either alkene isomer

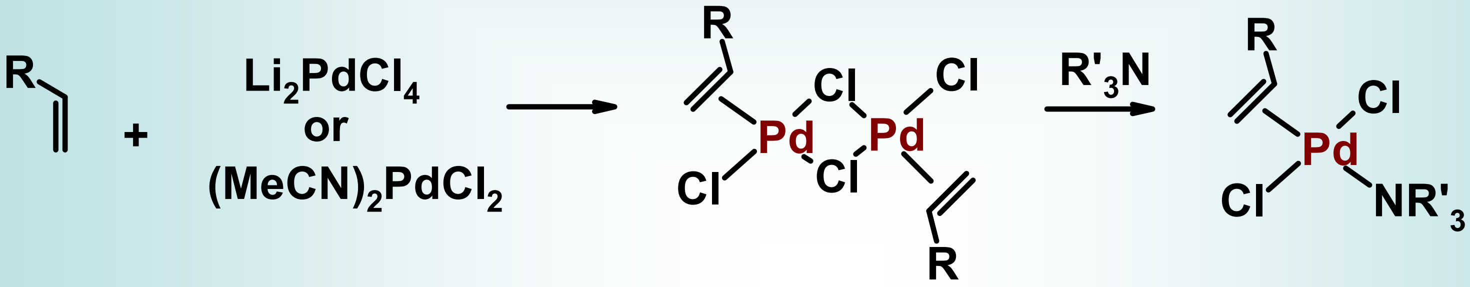


Pd^{II} Complexes of Alkenes

-probably the other major choice in alkene-TM complexes

Early Chemistry

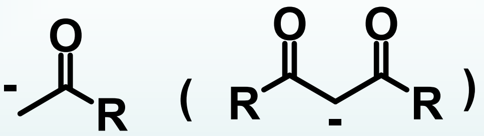
-Pd ^{II} forms comlexes with alkenes; an amine ligand is usually added to break up dimer and make a more reactive species



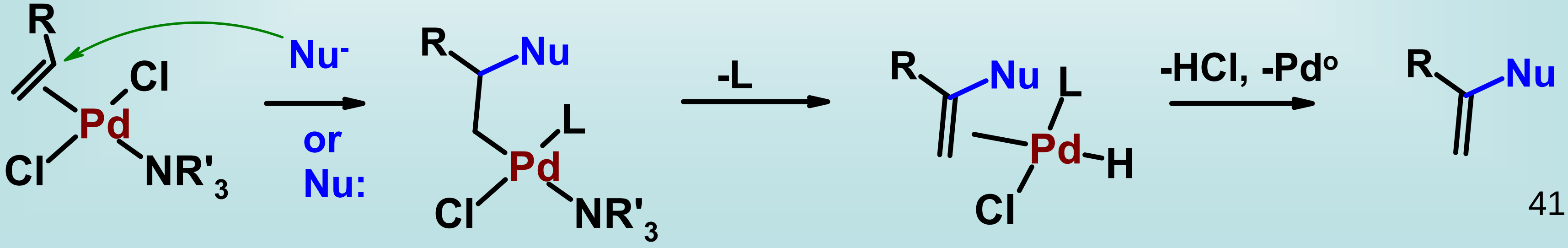
-susceptible to attack by nucleophiles on the more substituted C

-can sometimes reduce Pd off at low T, but mostly get β-H elimination

Nu:/Nu$^-$ = R_2NH, H_2O (ROH),



amines, water, alcohols, enolates



BUT......This is stoichiometric in Pd, and $PdCl_2$ 1g, \$102; 25g, \$1155

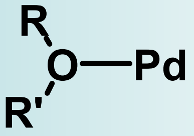
see, R Hegedus p.188-201
R Handbook of Organopalladium Chemistry for Organic Synthesis V2, Ch V3
Holton, R.A. *J. Am. Chem. Soc.* 1985, *107*, 2127 (chelating amines/sulphides)

However, if one has a stoichiometric oxidant present to oxidize the Pd° back to Pd^{II}, the could in principle be catalytic

- this can work: oxidant is most often O_2 or benzoquinone (BQ), or Cu^{II}

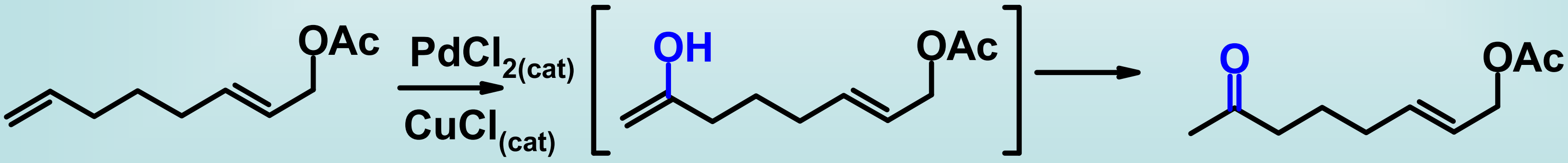
Earliest Successes

- is with oxygen based nucleophiles (H_2O, ROH)
-perhaps because oxygen nucleophiles don't displace the alkene ligand



and R−O−Pd are not tremendously strong interactions

-traditional version, with water as nucleophile, is called the Wacker process



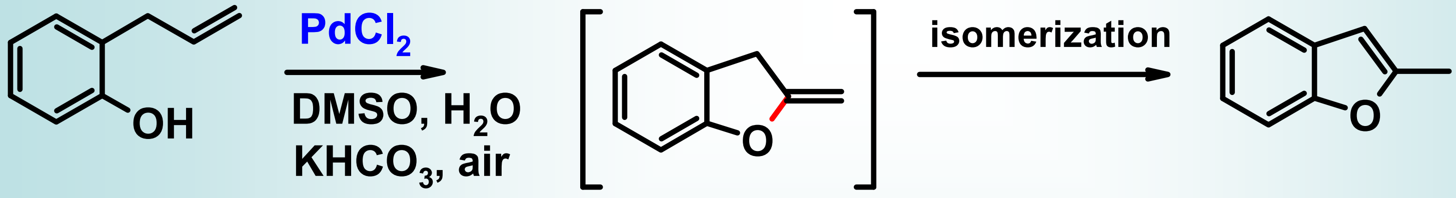
actually not true species

-reaction is selective for terminal alkenes; in fact intermolecular reactions for internal alkenes work poorly in most cases (*except* strong EWG substituted ones)

-<u>Markovnikov</u> addition - Nu: attacks most substituted side of the alkene normally
-this can be overridden by coordinating groups within the substrate

-$CuCl_2$ oxidizes Pd^o back to Pd^{II}; O_2 oxidizes Cu^I back to Cu^{II}

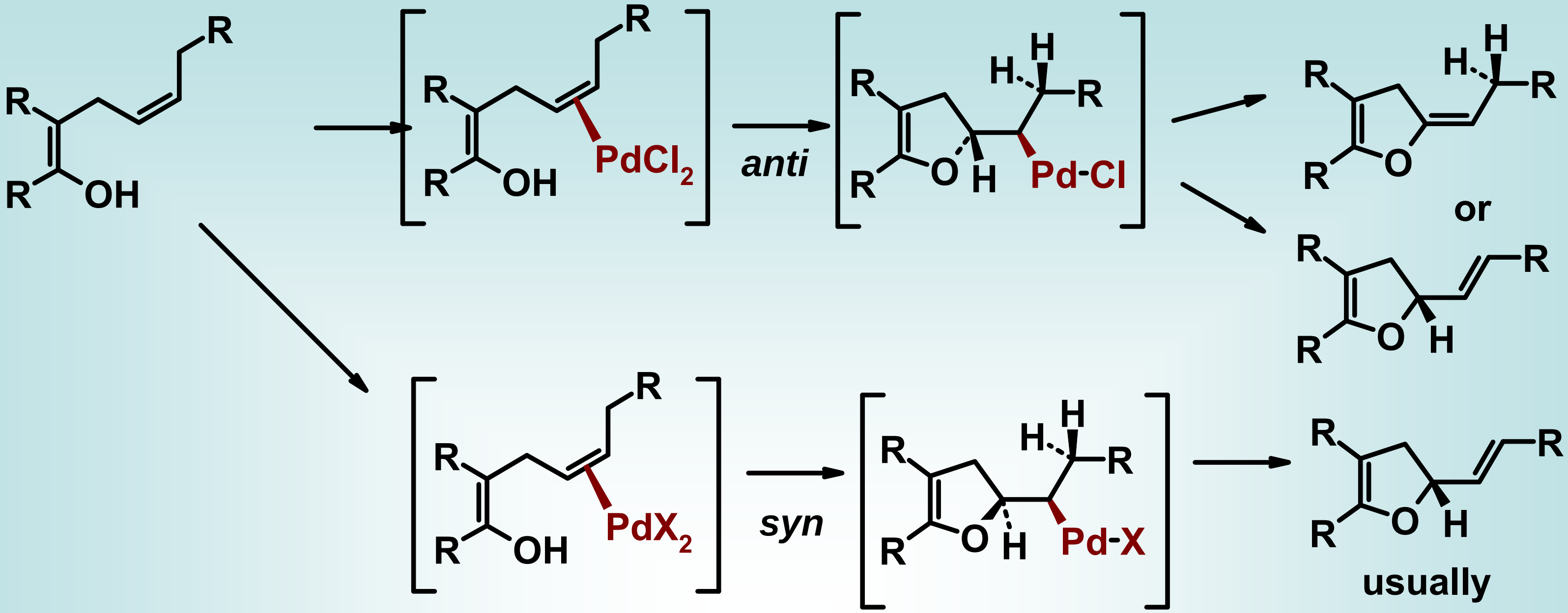
Alcohols and phenols can do this type of chemistry too, usually as an intramolecular addition



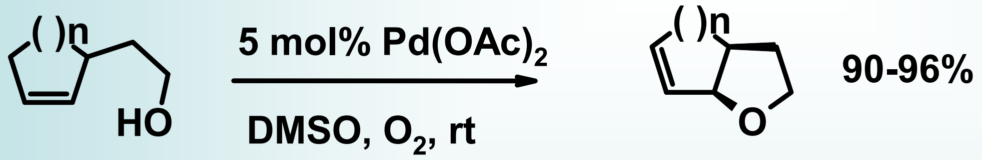
-normal tendency is to form 5- membered ring over 6- membered ring; this tendency can be overriden in some cases

- first work was with $PdCl_2$ as the Pd^{II} source, but now it is often replaced with other Pd^{II} salts

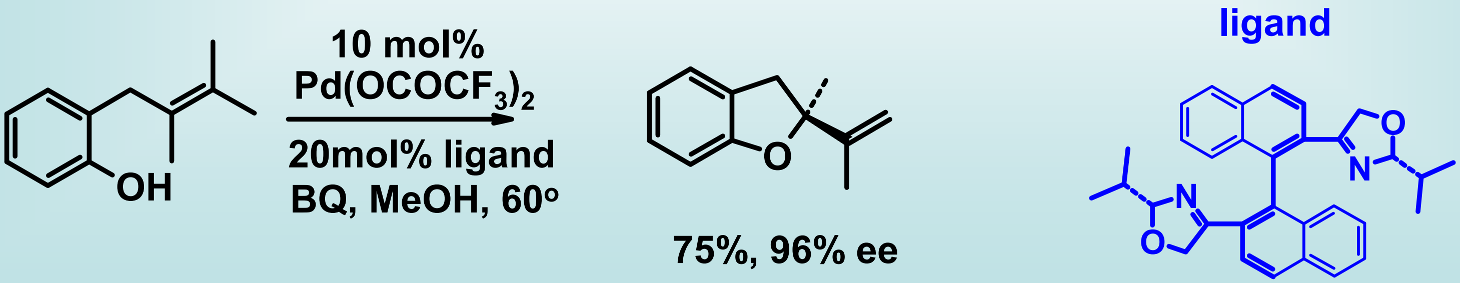
-Reason - with Cl^- salts, attack of Nu is *anti* to Pd; whereas with $Pd(OAc)_2$, $Pd(OCOCF_2)_2$, attack is *syn* to Pd
-*syn* attack allows/forces β-H elimination <u>away</u> from ring



Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* 2004, *126*, 3036.



-this even allows asymmetric synthesis at the newly formed chiral centre



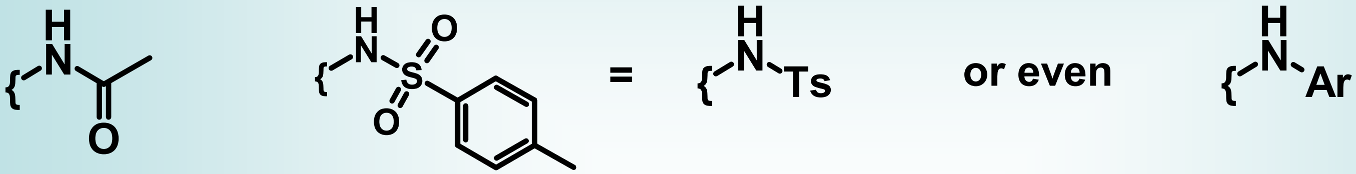
Uozumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* 1998, *63*, 5071

N Nucleophiles

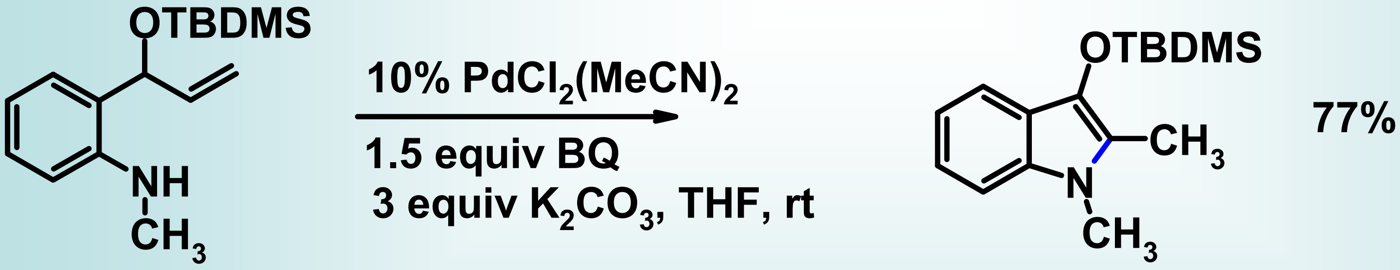
-sometimes called aza-Wacker

-problem with amine ligands - these are generally too basic/nucleophilic; tend to displace alkene as ligand

-as a result, in the vast majority of successful cases, the lone pair on N is deactivated



- with this restriction, this has become an increasingly important way of making heterocycles; especially possible for indole type systems

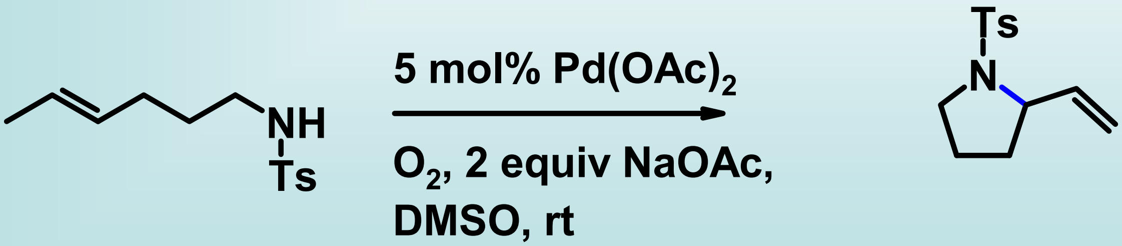


10% $PdCl_2(MeCN)_2$

1.5 equiv BQ

3 equiv K_2CO_3, THF, rt

77%



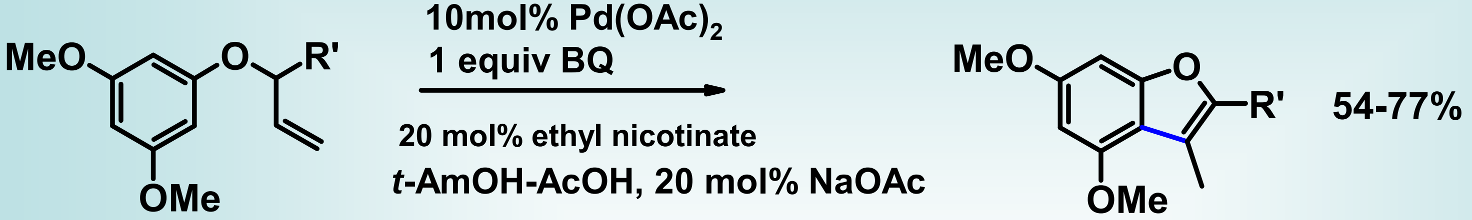
5 mol% $Pd(OAc)_2$

O_2, 2 equiv NaOAc, DMSO, rt

R Minatti, A.; Munoz, K. *Chem. Soc. Rev.* 2007, *36*, 1142.

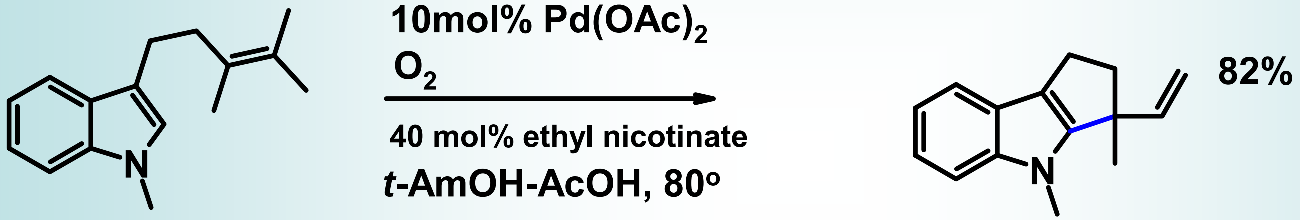
Carbon Nucleophiles

-success in these nucleophilic attack reactions has even been extended to carbon based nucleophiles such as silyl enol ethers, enolizable β-dicarbonyls, electron rich aromatics and heterocycles - there are even <u>some</u> intermolecular cases



10mol% Pd(OAc)$_2$
1 equiv BQ
20 mol% ethyl nicotinate
t-AmOH-AcOH, 20 mol% NaOAc

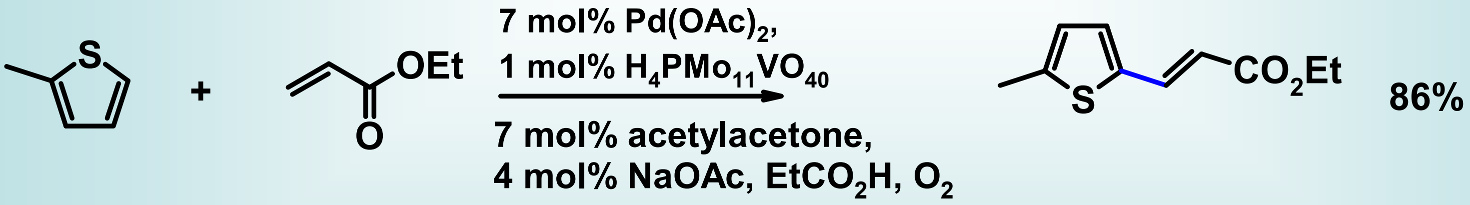
54-77%



10mol% Pd(OAc)$_2$
O$_2$
40 mol% ethyl nicotinate
t-AmOH-AcOH, 80°

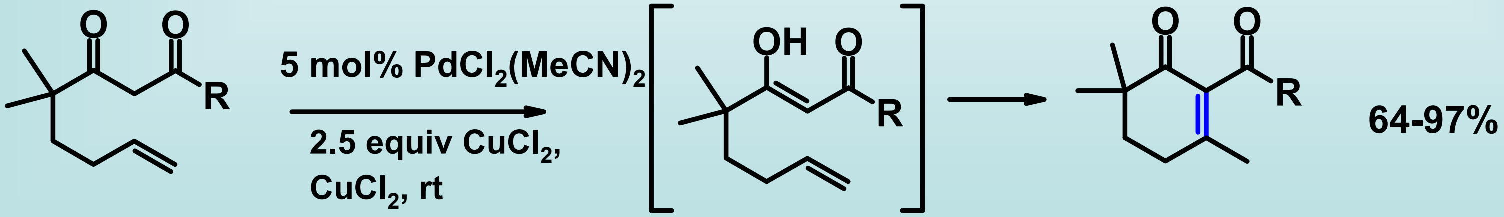
82%

Ferreira, E. M.; Stoltz, B. M.* *J. Am. Chem. Soc.* <u>2003</u>, *125*, 9578.



7 mol% Pd(OAc)$_2$,
1 mol% H$_4$PMo$_{11}$VO$_{40}$
7 mol% acetylacetone,
4 mol% NaOAc, EtCO$_2$H, O$_2$

86%

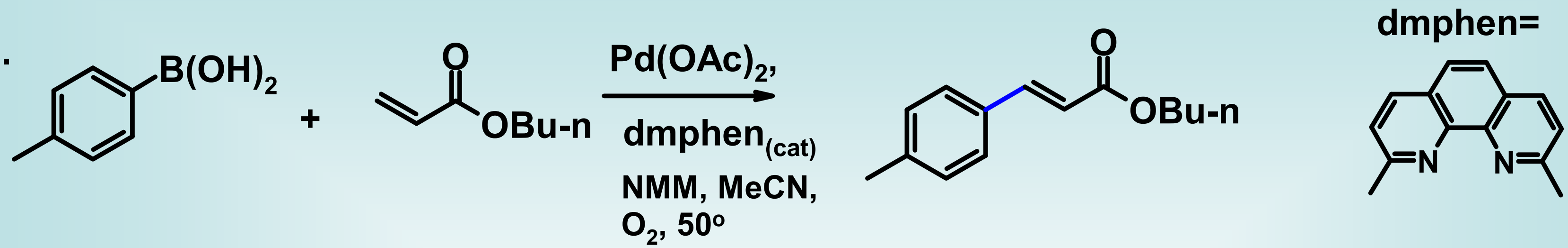


5 mol% PdCl$_2$(MeCN)$_2$
2.5 equiv CuCl$_2$,
CuCl$_2$, rt

64-97%

even organometallics, i.e., Ar-HgOAc (ancient history), ArB(OH)$_2$, ArSnR'$_3$

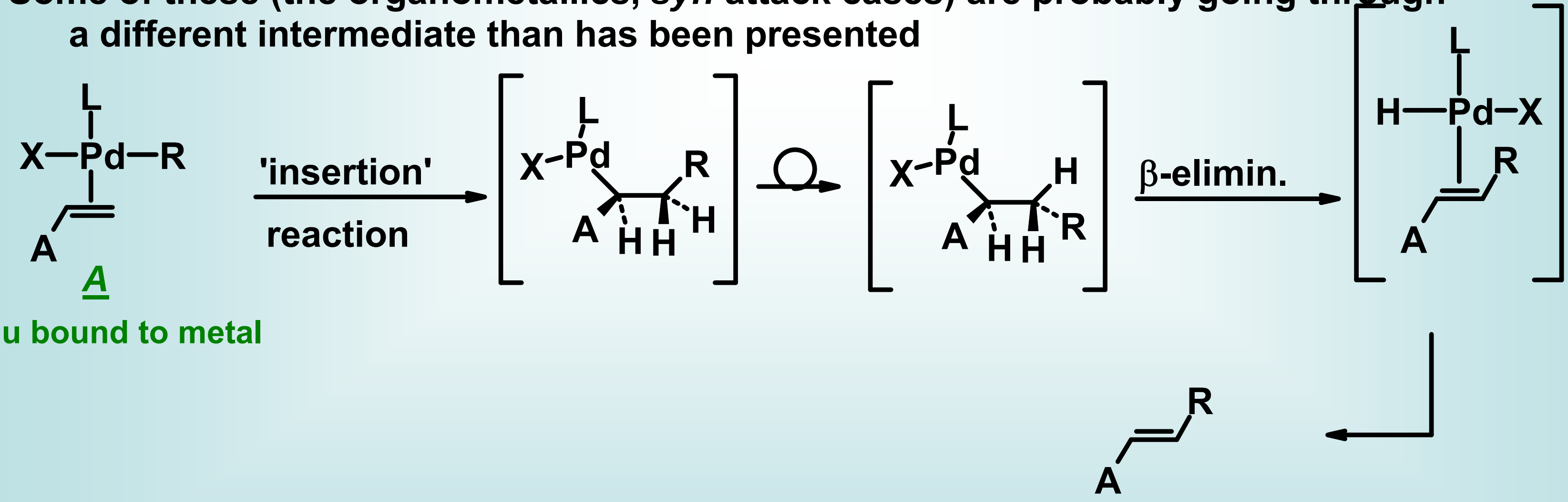
i.e.



exhaustive review **R** Becalli, E. M.; Broggini, G.; Martinelli, M.; Sottocomola, S. *Chem. Rev.* 2007, *107*, 5318.

We have been hiding an important point for a bit now, though

Some of these (the organometallics, *syn* attack cases) are probably going through a different intermediate than has been presented



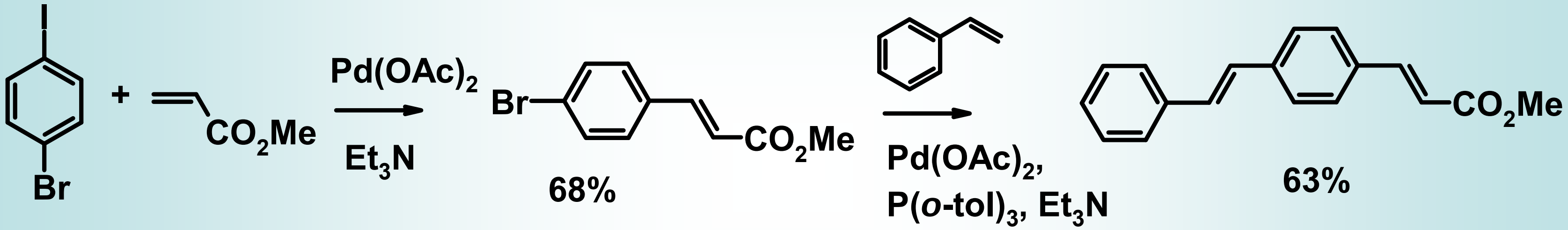
A

Nu bound to metal

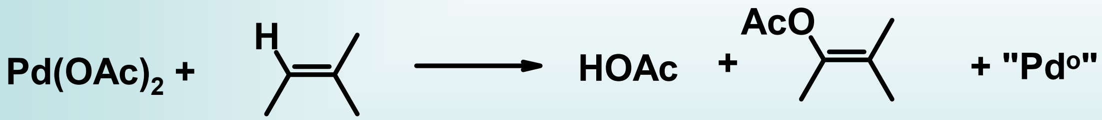
-much more common way to get at the intermediates ***A***
-by oxidative addition of Pd° to organic halides/triflates
-called **Heck reaction**

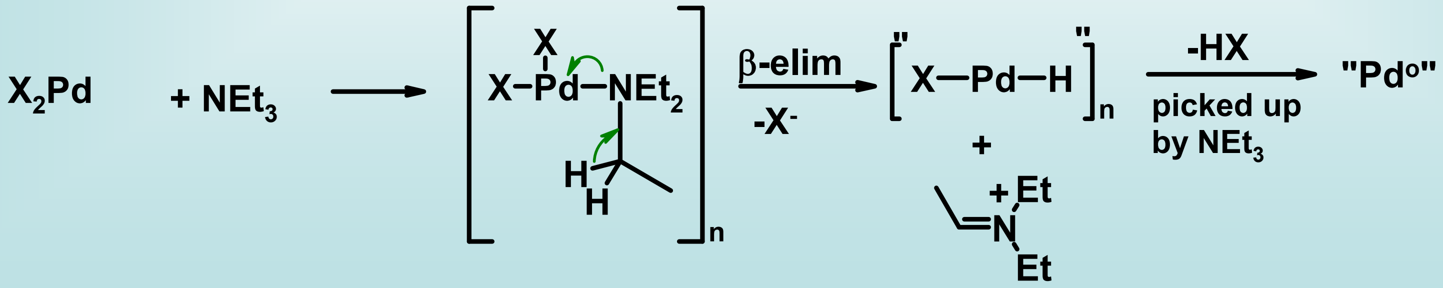
Reveiws - many

R Heck, R.F. *Org, React.* 1982, *27*, 345; *Acc. Chem. Res.* 1979, *12*, 146.
R Larock, *Adv. Met-Org. Chem.* 1994, *3*, 97.
R Jefery, T. *Adv. Met. Org. Chem.* 1996, *5*, ch.4.
R Crisp, G. T. *Chem. Soc. rev.* 1998, *27*, 427. (mechansitic detail)
R Knowles, J. P.; Whiting, A. *Org. Biomol. Chem*. 2007, *5*, 31 mechanistic detail
R De Vries, J. G. *Dalt. Trans.* 2006, 421 (mechanistic discussion)
R Ionso, F.; Beletskaya, I. P.; Yus, M.. *Tetrahedron* 2005, *61*, 11771.
R Miyaura, N. *Adv. Synth. Catal*. 2004, *346*, 1522.
R Jutand, A. *Pure Appl. Chem*. 2004, *76*, 565 (mechanistic detail)
R Dounay, A. B.; Overman, L. E. *Chem. Rev.* 2003, *103*, 2945 (asymmetric synthesis)
R Link, J. T. *Org. React*. 2002, *60* 157 (intramolecular rxns)



So now we need Pd^o, but we added Pd^{II}
Not a typo; Pd^{II} complexes often used and reduced *in situ*





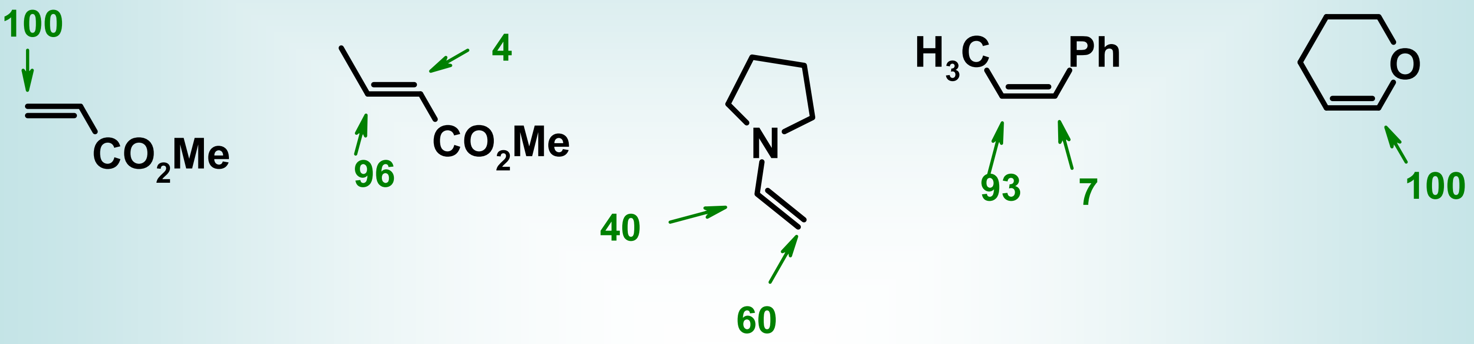
Regiochemistry

-somewhat different than intermolecular cases

-some tendency to go away from EWG's and towards EDG's, but sterics now (apparently) dominates

-Nu: goes 'towards' the less substituted site

i.e.



Stereochemistry

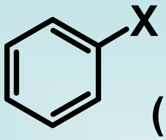
-resulting alkene is usually the most thermodynamically stable one, meaning *trans* ......all else being equal

Nature of the Organic Halide

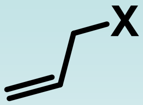
R-X (usually) can't have β-hydrogens on an sp^3 carbon atom, because of β-elimination

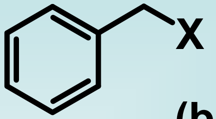
β-elimination takes place before any coupling can occur

Thus


(aryl)


(vinyl)


(allyl)

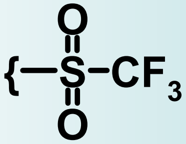

(benzyl)

Halides

-Br is most common choice

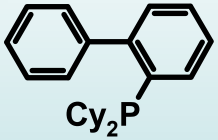
-I faster at oxidative addn, but more side rxns
(sometimes better, sometimes worse)

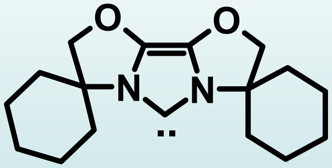
-triflates are excellent pseudohalides

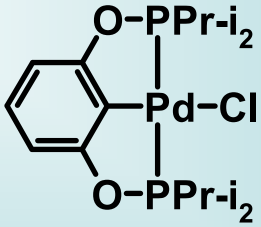

$$\{-\overset{\displaystyle O}{\underset{\displaystyle O}{\overset{\|}{\underset{\|}{S}}}}-CF_3$$

-Cl historically sluggish, but coming along nicely with new catalysts, including sterically hindered phosphines, carbenes as ligands, and ortho- metallated palladacycles

i.e., P^tBu_3



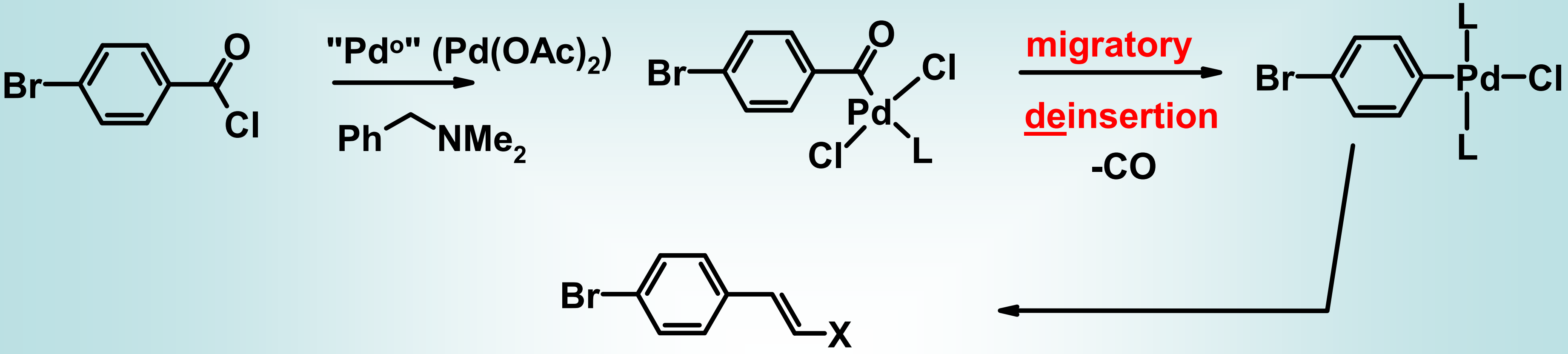




R Whitcome, N. J.; Hii, K. K.; Gibson, S. E. T*etrahedron* 2001, *57*, 7449.
R Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* 2002, *41*, 4176.
R Christmann, U.; Vilar, R.* *Angew. Chem. Int. Ed.* 2005, *44*, 366

A cute but increasingly irrelevant variation - acid chlorides

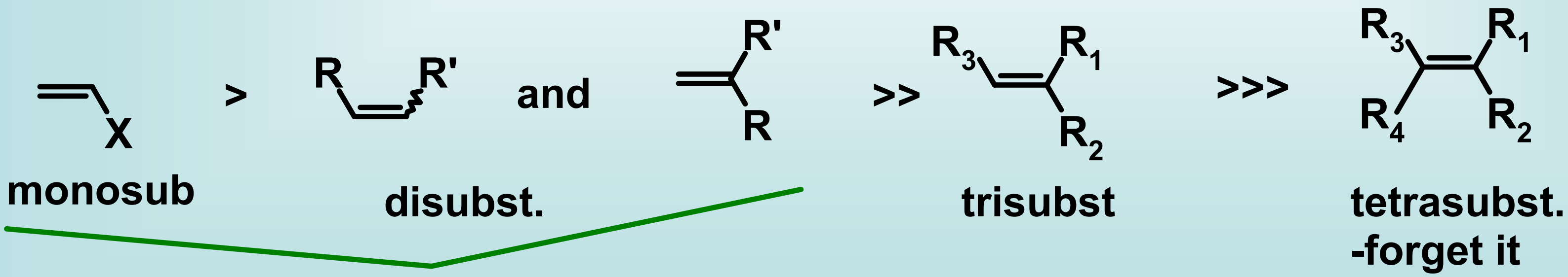
-aryl chlorides are very reactive to oxidative addition, and may be accessibe when the halides are not



-can occur under very mild conds, in some cases - being made obsolete by improvements to aryl chloride Heck reactions

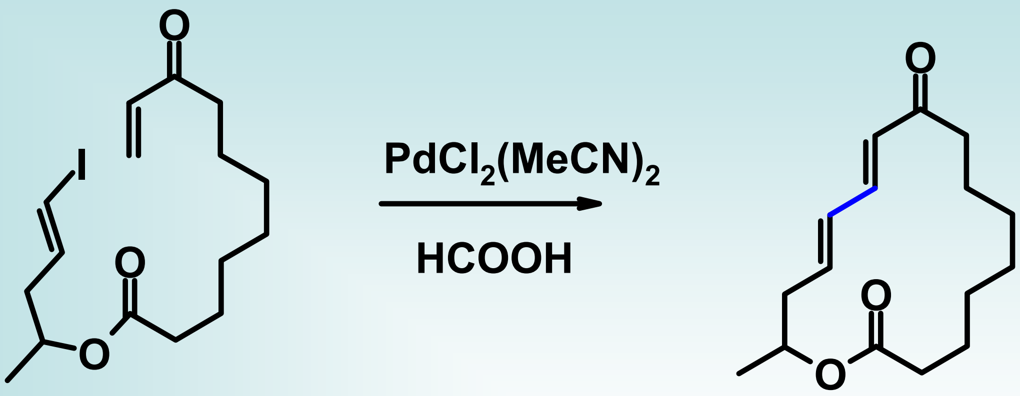
Spenser, A. *J. Organomet. Chem.* 1983, *247*, 113; 1984, *265*, 273.
Jeffery, T. *J. Chem. Soc., Chem. Commun.* 1984, 1287.
Tetrahedron Lett. 1985, *26* 2667.

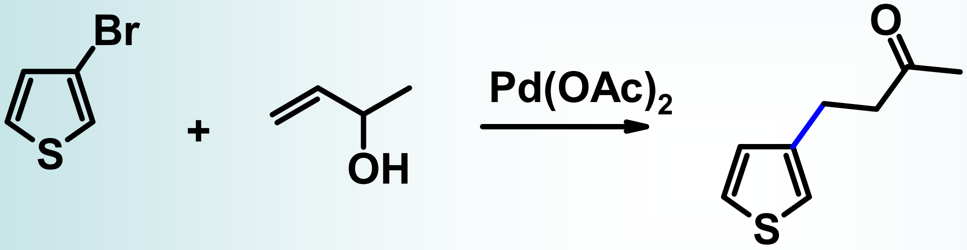
The Alkene



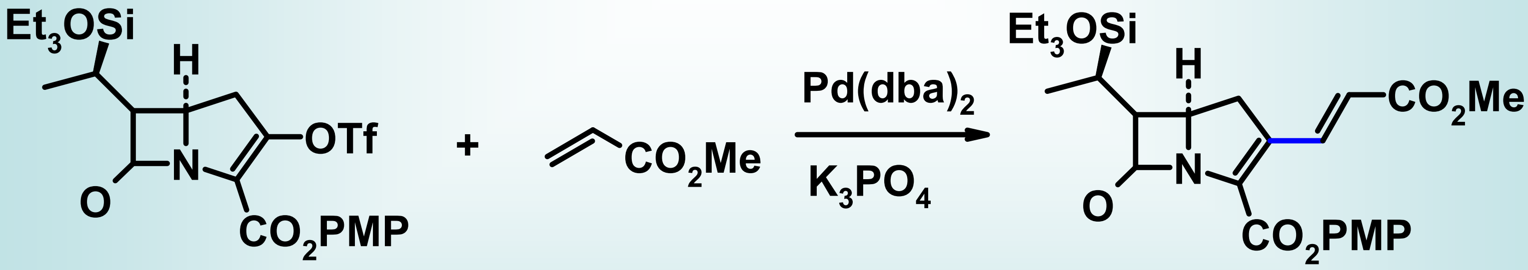
only practical ones

-ligands generally stabilize palladium intermediates, but are't always added
-inorganic base is often used (instead of amine) to consume H-X

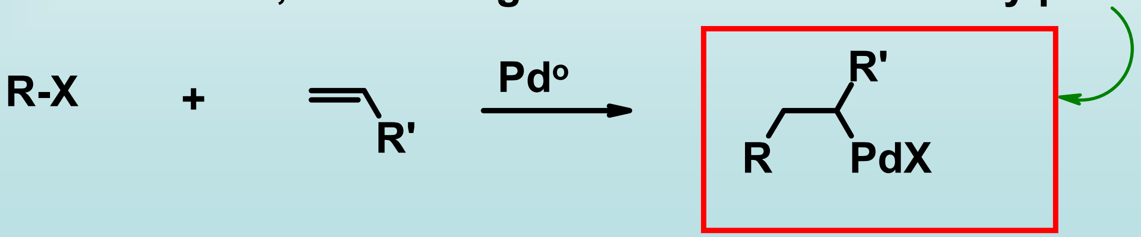




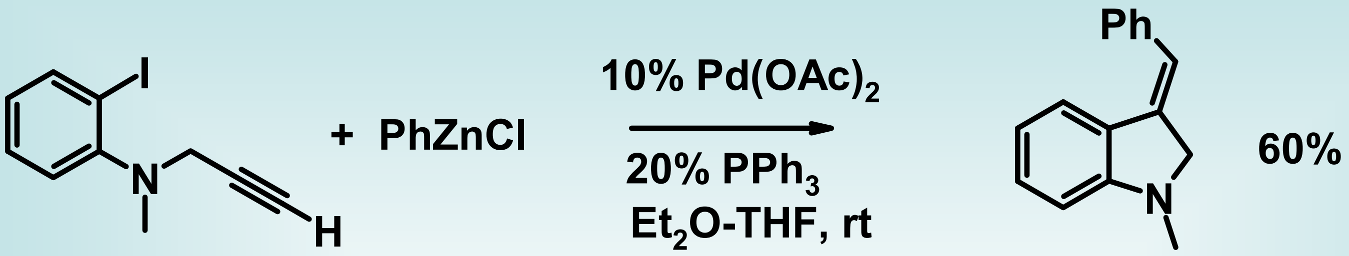
Note what happens to β-elimination process



In some cases, other things can be done to the alkylpalladium

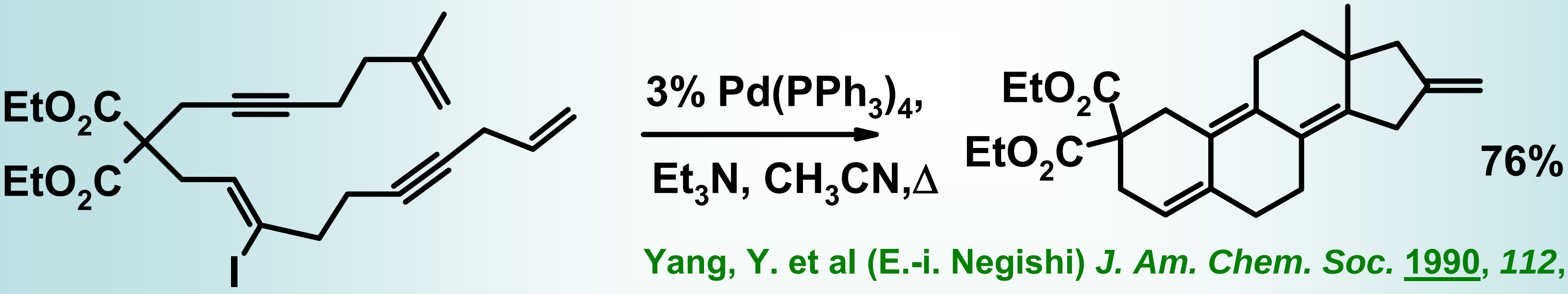


a) Trap with organometallics



Grigg, R. et al *Tetrahedron Lett*. 1990, *31*, 6573 & refs therein

b) Further cyclopalladation



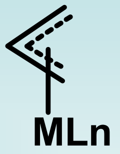
Yang, Y. et al (E.-i. Negishi) *J. Am. Chem. Soc.* 1990, *112*, 8590.

For still more reviews, see...

R Handbook of Organopalldium Chemistry for Organic Synthesis V1, Ch IV 2.4-2.6
R Naso, F.; Marchese, G., in The Chemistry of Halides, Pseudo Halides, and Azides;
Patai, S; Rappoport, Z. eds Ch. 26, Wiley 1983,
R Green, J. R. in The Chemistry of Halides, Pseudo Halides, and Azides, Supplement D2, Ch 25, Wiley 1995
R Shibasaki, M. Soden, C. D. Kojima, A. T*etrahedron* 1997, *53*, 7371
R Balme, G. Bouyssi, D.; Lomberget, T. Monteiri, N. *Synthesis* 2003, 2115

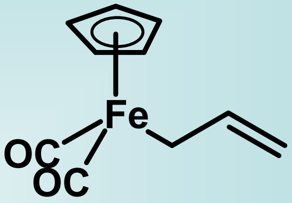
η^3- Hydrocarbon Metal Complexes

i.e.



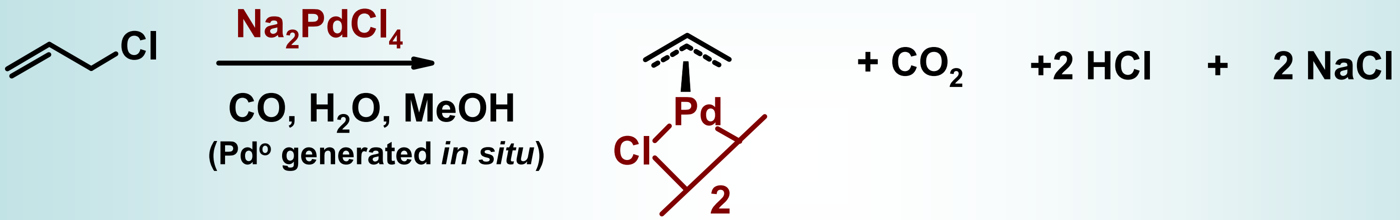
type complexes

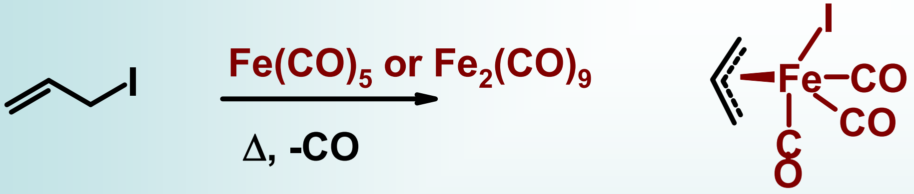
Note: We will discuss
these here, too;
even though they're
η^1

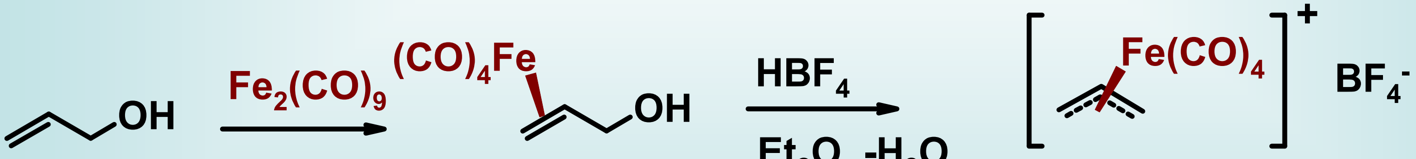


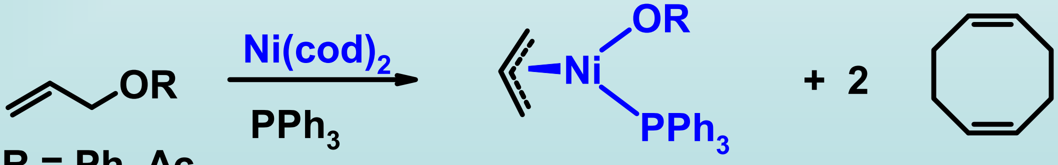
Preparation of η^3-allyl Complexes

i) From olefins (alkenes) with allylic leaving groups

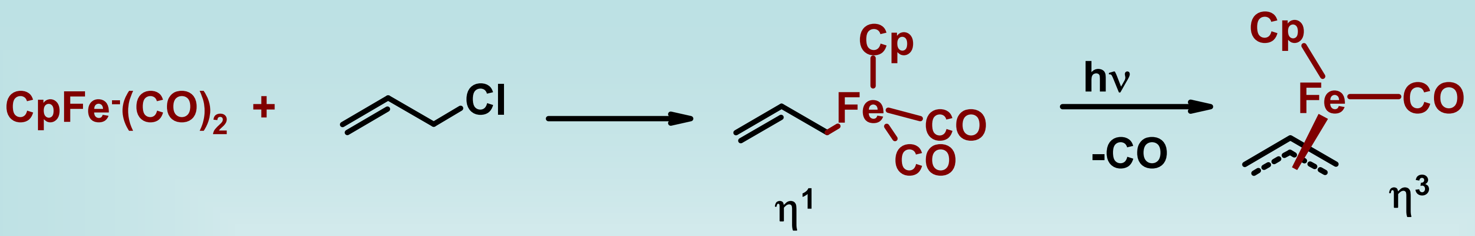




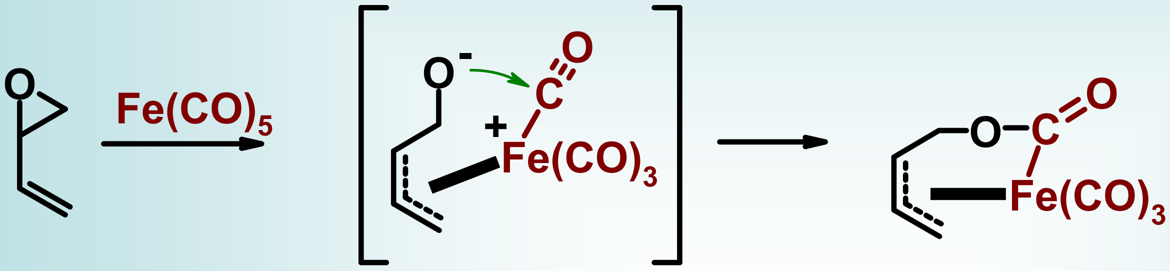




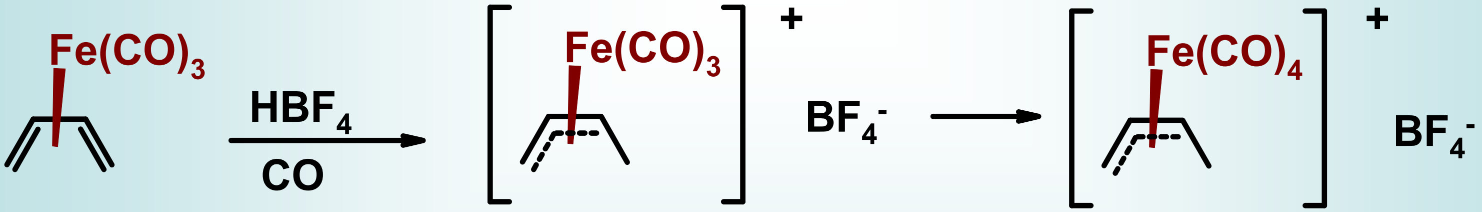
R = Ph, Ac



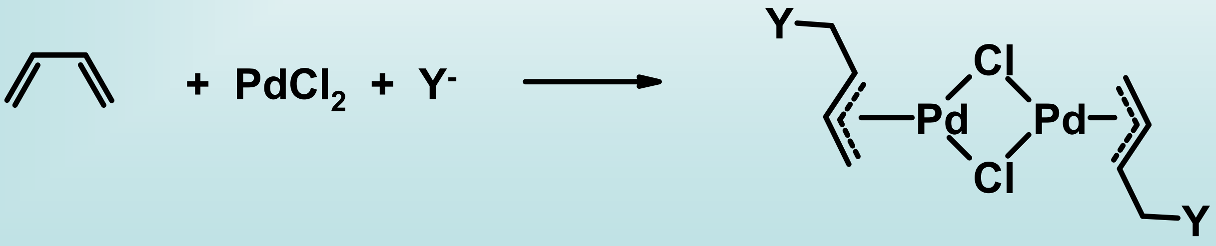
Fish, R. W. et al (Rosenblum) *J. Organomet. Chem.* 1976, *105*, 101.



ii) From Metal-Diene Complexes



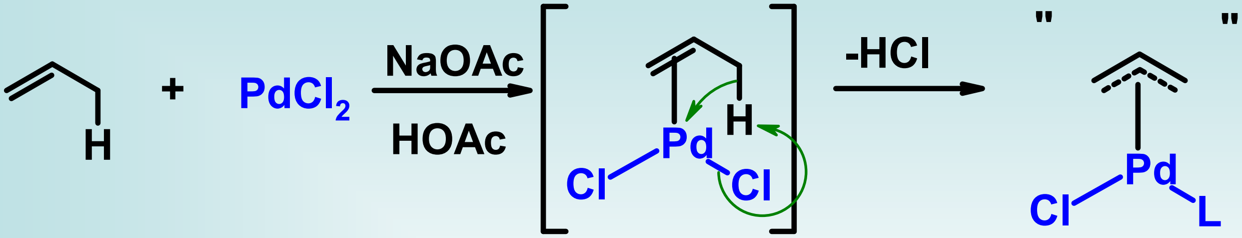
Salzer, A.*; Hafner, A. *Helv. Chem. Acta* 1983, *66*, 1774.



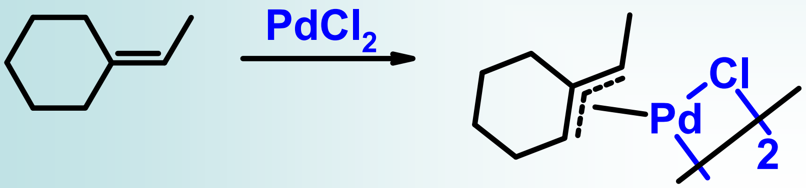
Y^- = Cl^-, RO^-,
AcO^-, PhHgCl

Trost, B. *Tetrahedron* 1977, *33*, 2615.

iii) Activation of allylic C-H Bonds
-most applicable for Pd complexes

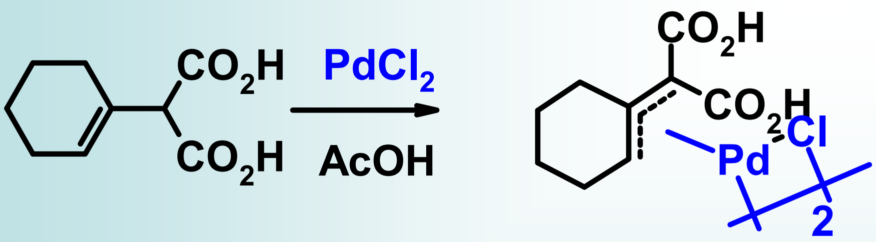


i.e.,



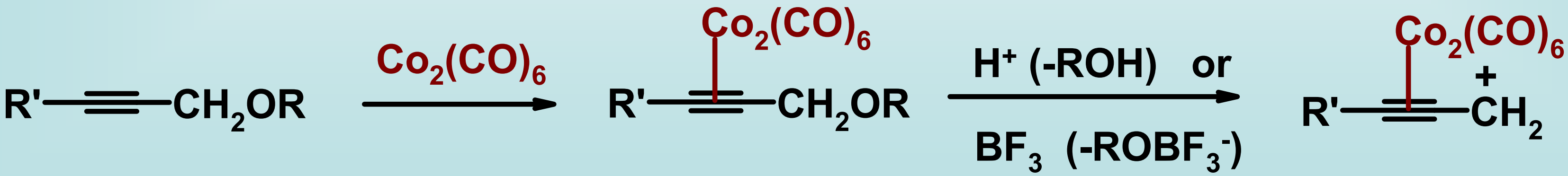
Trost, B. M. *Tetrahedron Lett.* 1974, 2603.

Huttl, R. *Chem. Ber.* 1968, *101*, 252.



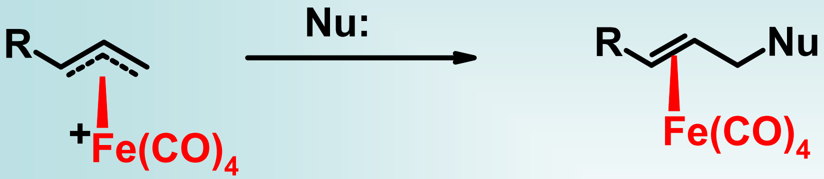
Chrisope, D. R.; Beak, P.; Saunders, W. H., *J. A. Chem. Soc.* 1988, *110*, 230

iv) Propargyl (di)Co complexes



Allyl/Propargyl η^3- Complexes as Electrophiles

a) Cationic allyl tetracarbonyl complexes



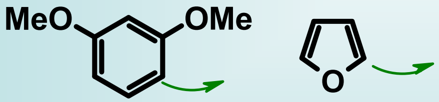
-complexes react with a pretty wide range of nucleophiles to give η^2-alkene complexes as immediate products

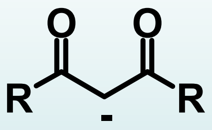
-these η^2-alkene complexes are not all that stable, easily decomplexed by mild oxidant

-allyl attack is presominantly at less substituted side of allyl unit (more later)

Nu: can be... R_3N (amines), Ph_3P (phosphines), R_2Cd (RMgBr), RCu(CN)ZnI

electron rich arenes, H^- (Et_3SiH),





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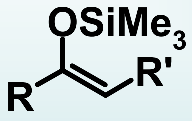

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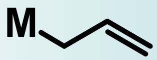


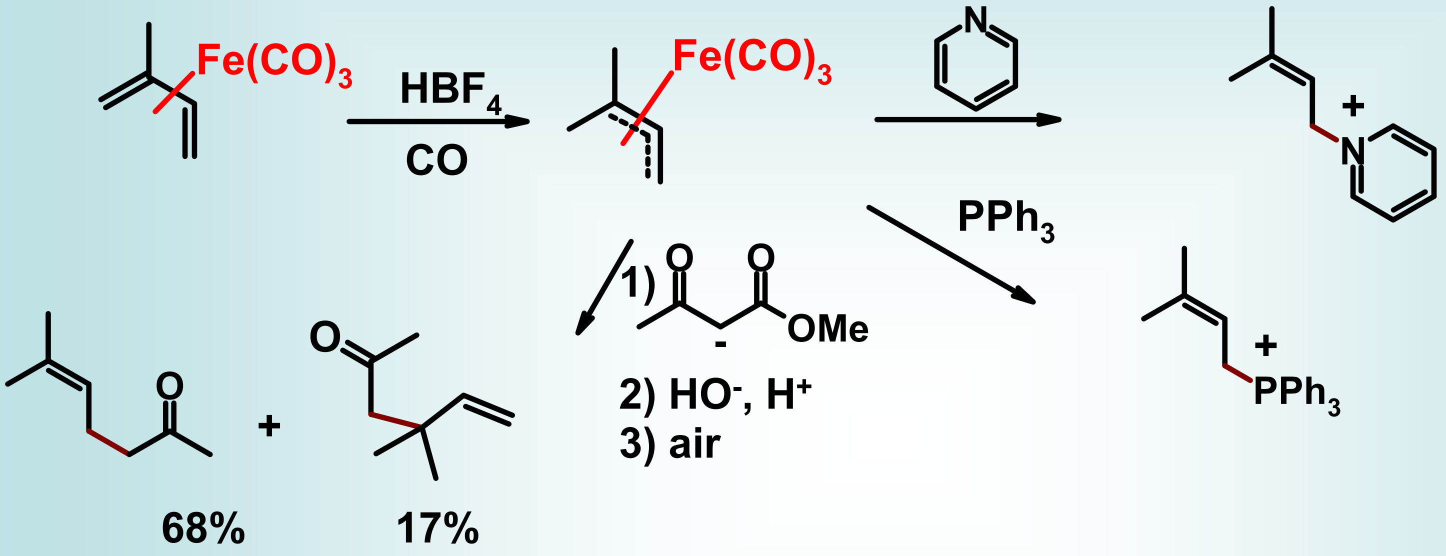
(M = Me_3Si, Bu_3Sn, R_2B)

R Pearson, A. J. "Iron Compounds in Organic Synthesis", Academic Press, 1994, Ch.3
R Green, J. R.; Donaldson, W. A., in "Encyclopedia of Inorganic Chemistry", Lukehart, C. M., ed., Wiley 1994, V 4, p. 1735.

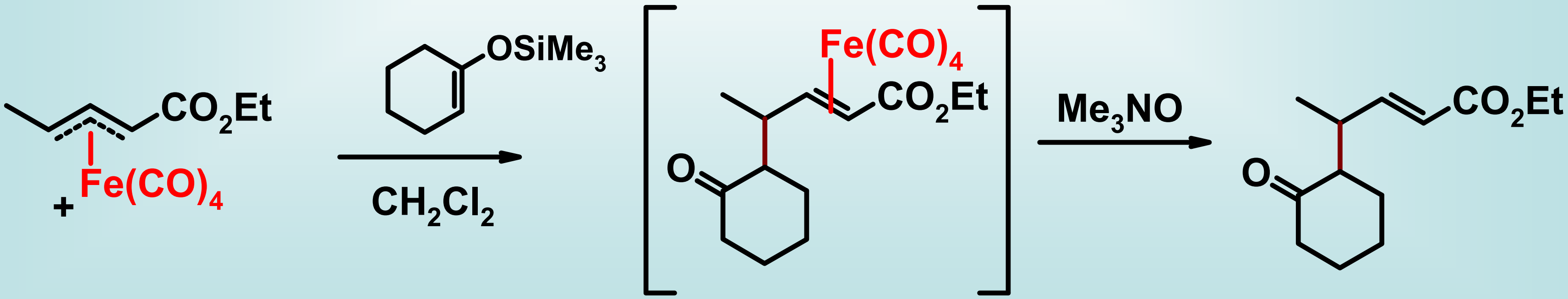
Regiochemistry

-Site of attack is normally at the less substituted end of the allyl unit

-C2 attack has never been observed



-Site of attack is away from electron withdrawing group



Green, J. R.*; Carroll, M. K. *Tetrahedron Lett.* 1991, *32*, 1141.

Why care?

-allyl cations are very highly reactive; either too unstable to prepare or too reactive to be isolated or control their reactivity

-site γ-to carbonyl is normally nucleophilic; therefore this is *umpolung* reactivity

-iron allyls are geometrically stable

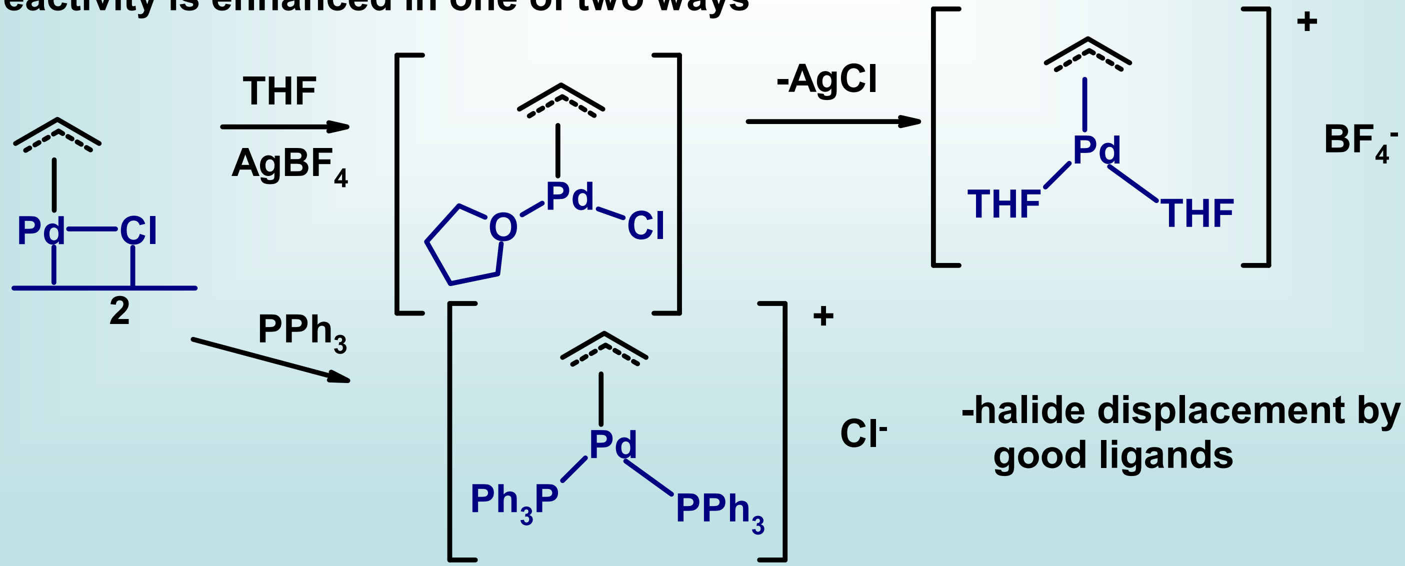
R de Koning, H.; Hiemstra, H.; Moolenar, M. J.; Speckamp, W. N. *Eur. J. Org. Chem.* 1998, 1729.
R Enders, D.; Jandeleit, B.; von Berg, S. *Synlett* 1997, 421.

b) Allylpalladium^{II} Complexes

Hegedus, p. 245 start
Tsuji, p. 116-168

-by FAR, the most widely used η^3-allylmetals
-like the Pd alkene complexes, the chloro- bridged dimers usually aren't reactive enough

-reactivity is enhanced in one of two ways

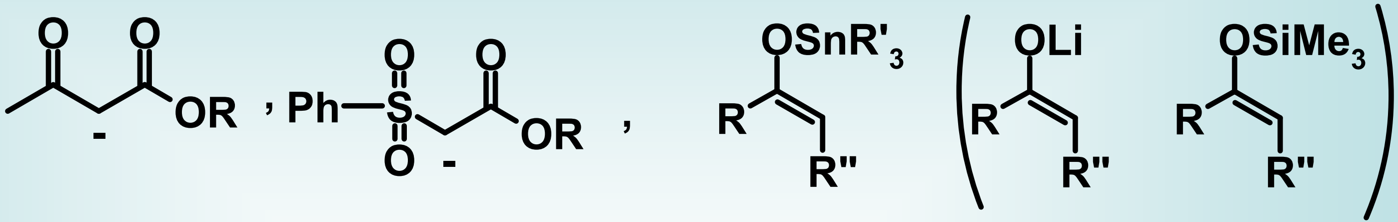


-halide displacement by good ligands

-can also be activated by other ligands (esp. phosphines), dimethyl sulphoxide (DMSO), hexamethylphosphoric triamide (HMPA)

- once 'activated', these can undergo nucleophilic attack by several reagents

AcO^-, R_2NH,



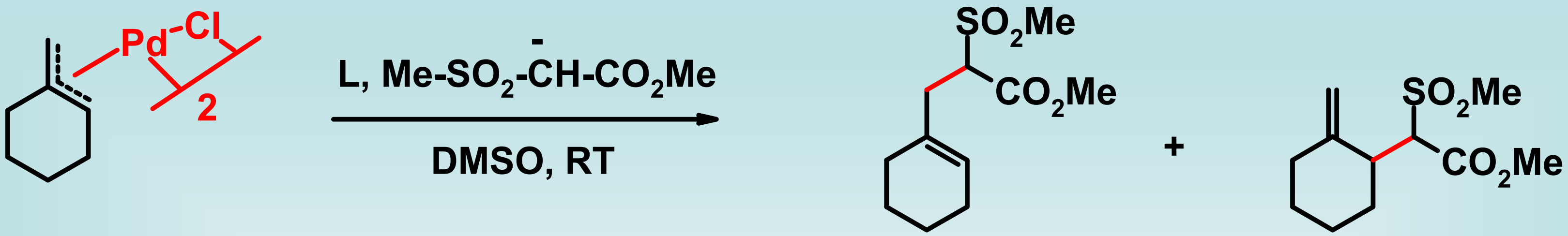
less reliable

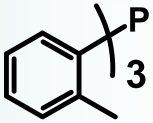
-attack superficially similar to allylirons
-i.e., normally at the less substituted allyl terminus
-this can, however, be affected by choice of phosphine ligand

-rationale - more electron rich C-Pd bond shouold be the stronger one - this is the more substituted one
- therefore the less substituted one is more weakly held, so Nu^- attacks there

-BUT , with a bigger ligand (i.e., (*o*-tol)$_3$P), there is a steric repulsion between PdL_2 and the more substituted C - makes that bond <u>weaker</u>, more easily attacked

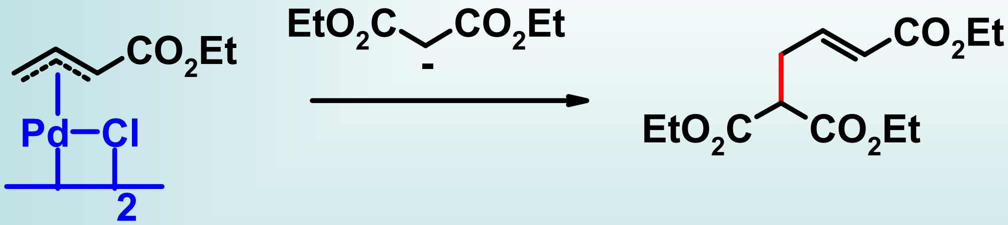
Consider.....

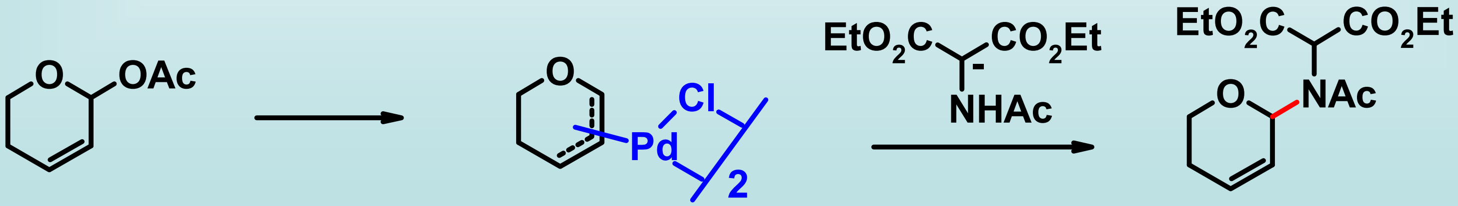


L		
PPh_3	62	38
n-Bu_3P	100	0
	18	82

Trost, B. M. et al *J. Am. Chem. Soc.* 1978, ***100***, *3416.*

-electron withdrawing groups direct attack to the end site remote to the group
-electron donating groups direct attack to the end near the EDG

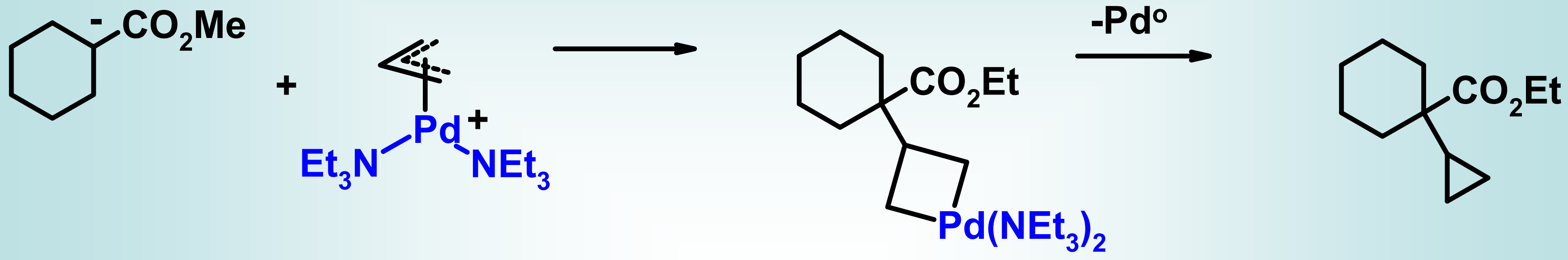




-there are rare cases of attack at the <u>central</u> carbon of the allyl unit - C-2 attack

-usually observed for Nu^- with high pKa's (20-30), or where the central carbon has a leaving group

-C-2 attack has very limited use in synthetic organic chemistry so far

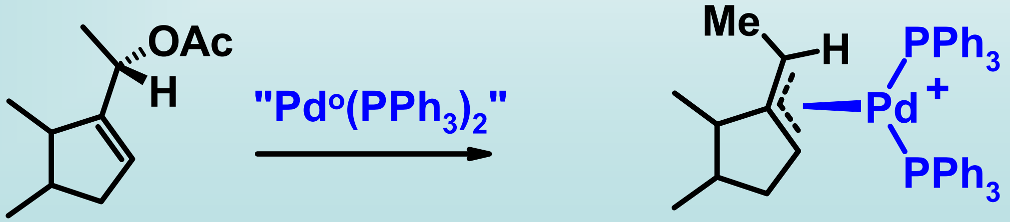


-for a good discussion and lead refs, see...

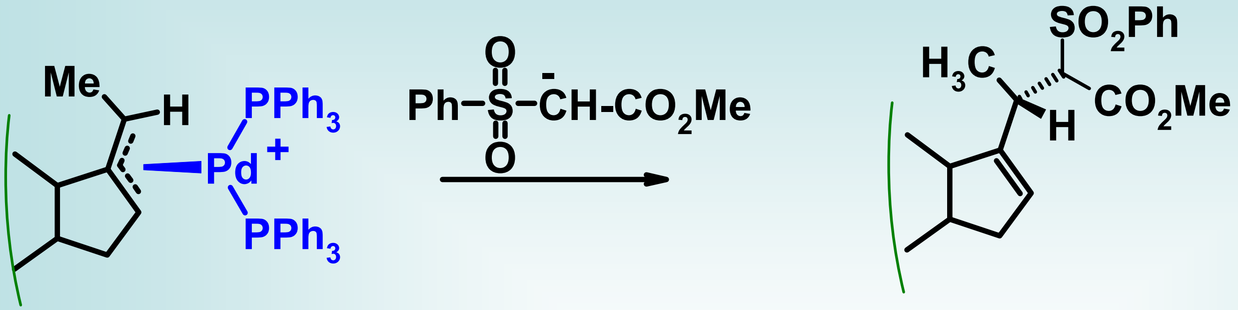
Aranyos, A., et al (Backvall, J. R.) *Organometallics* <u>1997</u>, *16*, 1058.
Organ, M. et al *J. Am. Chem. Soc.* <u>1998</u>, *120*, 9283.

Stereochemistry of Attack

-recall - oxidative addition to for π- allyl is on a alkyl centre, and therefore goes with <u>inversion</u> of configuration

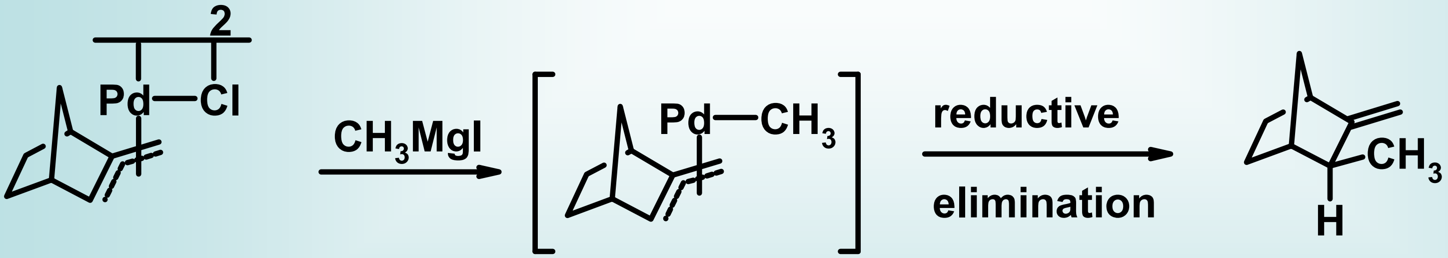


-now, nucleophilic attack on the allylpalladium normally occurs *away* from the palladium (it could be called backside attack, too), so overall there is a retention of configuration at carbon



Note: This is the normal (and ideal) situation
non-stabilized carbanions are not usually good for attack on these species;
when the do work, the mechanism is different....

- then, the initial attack step is on the metal, which is followed by reductive elimination to give retention for this step

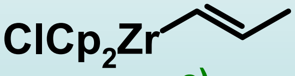


Nu⁻ = MeMgX,

a)

b)

PhMgBr

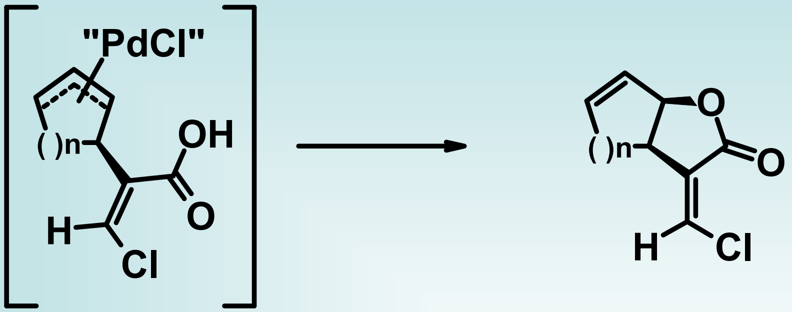


c)

Tetrahedron Lett. 1979, 3221
J. Chem. Soc., Chem. Commun. 1984, 107
b) *Organometallics*, 1985, *4*, 417

J. Organomet. Chem. 1975, *102*, 359
a) *J. Am. Chem. Soc.* 1984, *106*, 5028.
c) *J. Am. Chem. Soc.* 1982, *104*, 1310 and 5028.

-Acetate/carboxylate will attack with retention under special conditions, or if forced by the constraints of the molecule

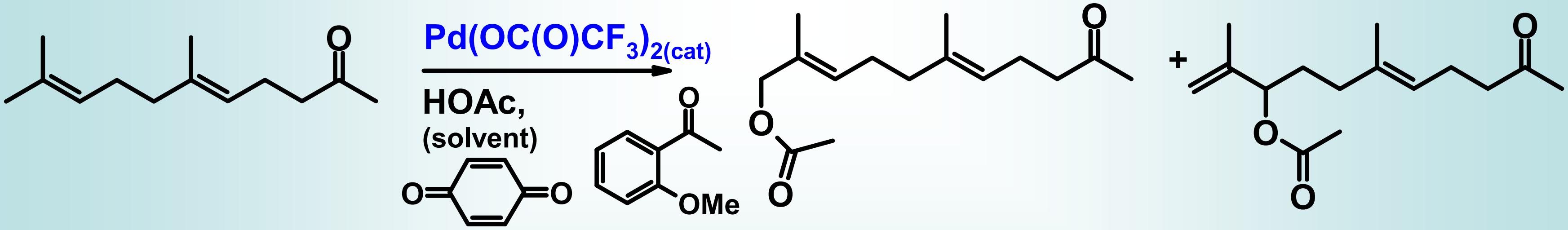


Larock, R.C. *J. Org. Chem.* 1984, *49*, 3662.

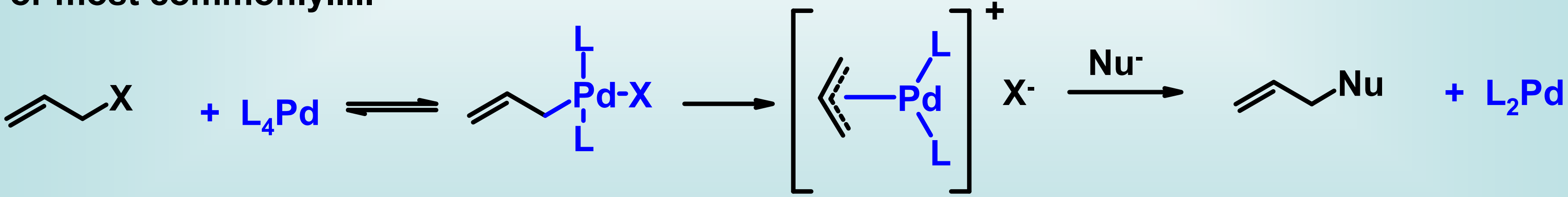
The best news is that many, many, many of these reactions can be done as catalytic reactions

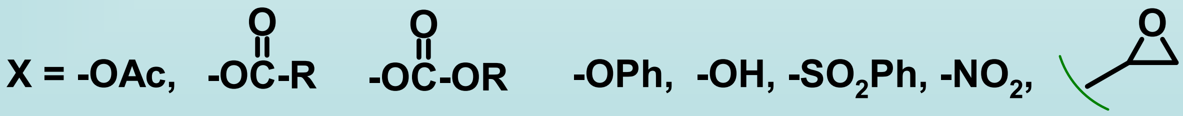
for example, allylic oxidation

McMurry, J. R.; Kocovsky, P. *Tetrahedron Lett.* 1984, *25, 4187.*

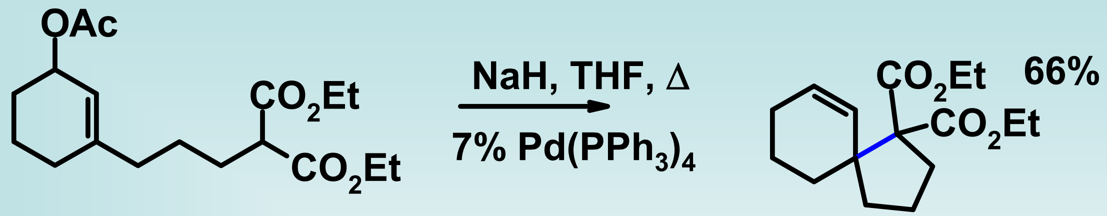


or most commonly.....

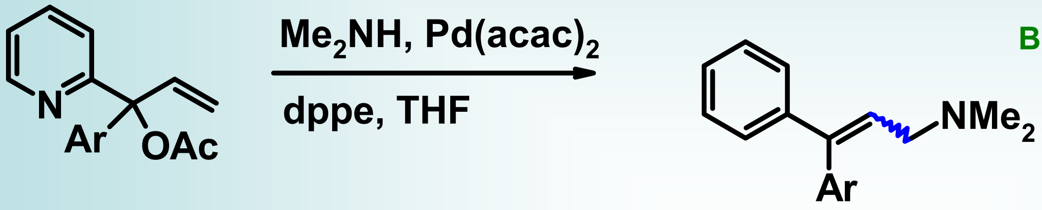




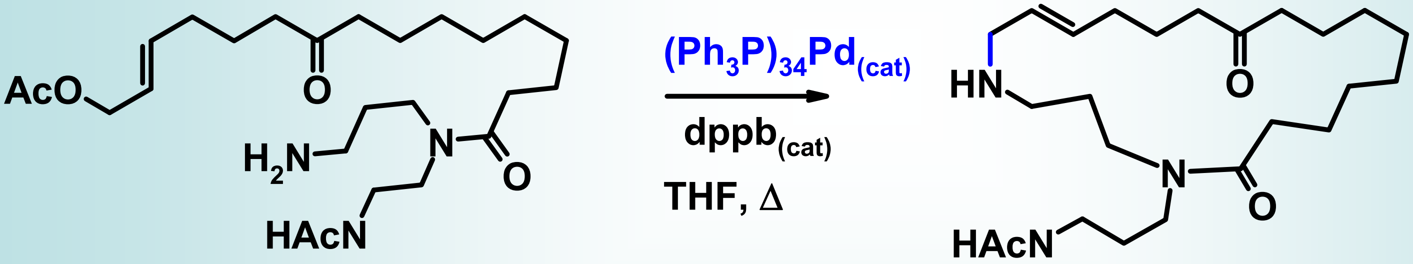
X = -OAc, $-OC(=O)-R$, $-OC(=O)-OR$ -OPh, -OH, $-SO_2Ph$, $-NO_2$, so......



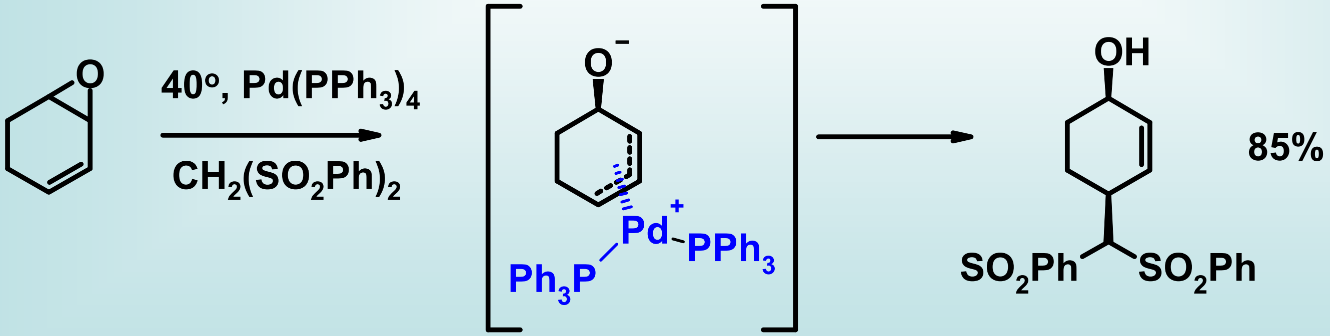
Godleski, S. A.;Valpey, R. S.
J. Org. Chem. 1982, *47*, 381.



Backvall, J. R. *J. Org. Chem.* 1981, *46*, 3479.



Trost, B.M.; Cossy, J. *J. Am. Chem. Soc.* 1982, *104*, 6881.



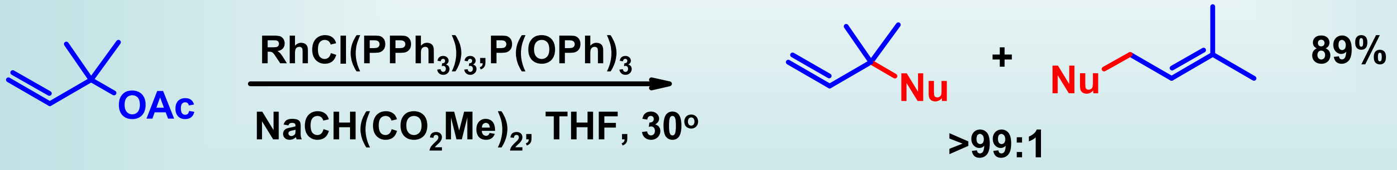
Notes on that last one: 1) Allylic substituent, CHR-OH is electron withdrawing <u>and</u> sterically blocking 'proximal' attack - therefore, attack is on remote (distal) end of allyl unit

2) Oxidative addition goes with inversion
Nucleophilic attack is from backside of Pd allyl = inversion
so overall <u>retention</u>

Question: How about the other possible regiochemical outcome, i.e., attack at more substituted end?

If you instead use Co group catalysts, particularly Rh^{I} and Ir^{I}, and use less donating ligands (phosphites, esp. P(OPh)$_3$), it is clear that allyl more 'electrophilic', so location of '+' resonance for more critical - attack on more substituted end.

<u>R</u> Takeuchi, R. *Synlett* <u>2002</u>, 1954 (Ir)



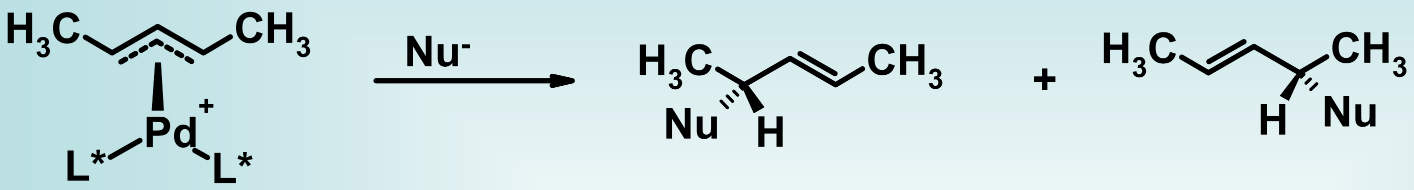
<u>R</u> Leahy, D. K.; Evans, P. A. Modern Rh-Catalyzed Organic Reactions, Ch. 10

-Other metal systems such as Ir^{III}, Mo^{II} can do similar substitutions

<u>R</u> Krska, S. W. et al (+Trost, B. M.); Pure Appl. Chem. <u>2004</u>, 76, 625.(Mo)

Enantioselectivity

-most of the work has been done on allyls with symmetrical substitution patterns, using a chiral ligand

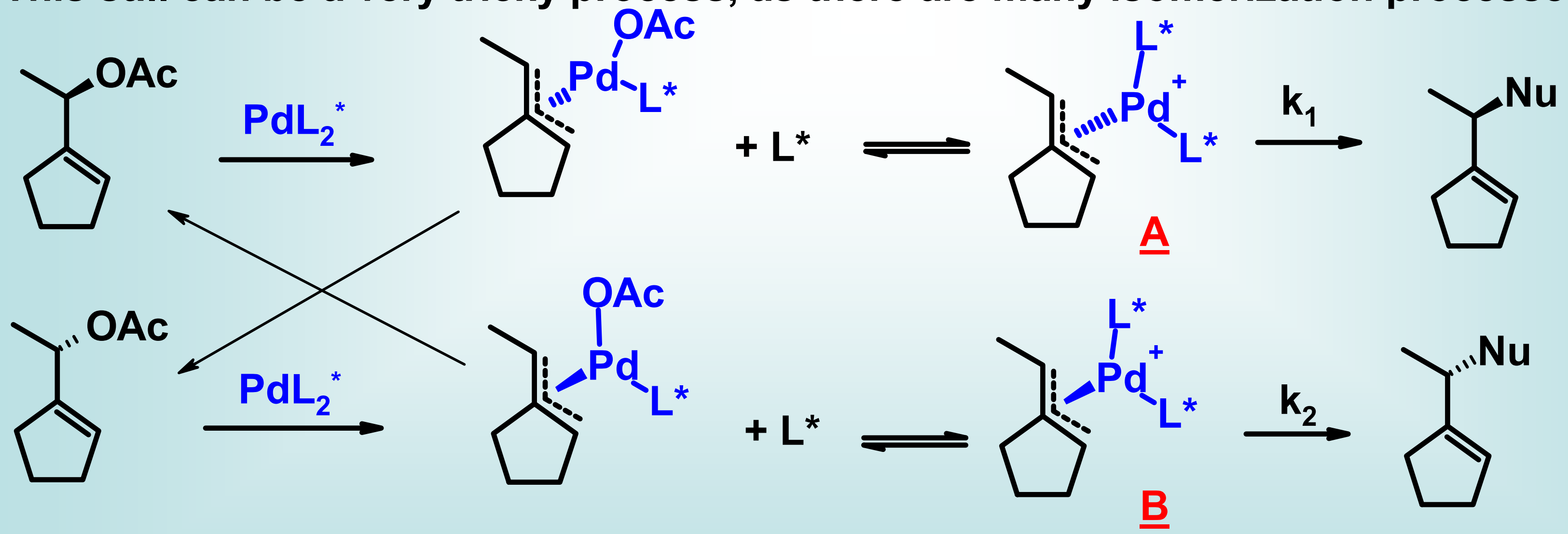


$Nu^- = {}^-CH(CO_2Et)_2$ especially

Most recent reviews

<u>R</u> Trost, B. M. *J. Org. Chem.* <u>2004</u>, *69*, 5813.
<u>R</u> Trost, B. M. *Chem. Rev.* <u>2003</u>, *103*, 2921.
<u>R</u> Graening, T.; Schmalz, H.-G. *Angew. Chem. Int. Ed.* <u>2003</u>, *42*, 2580.

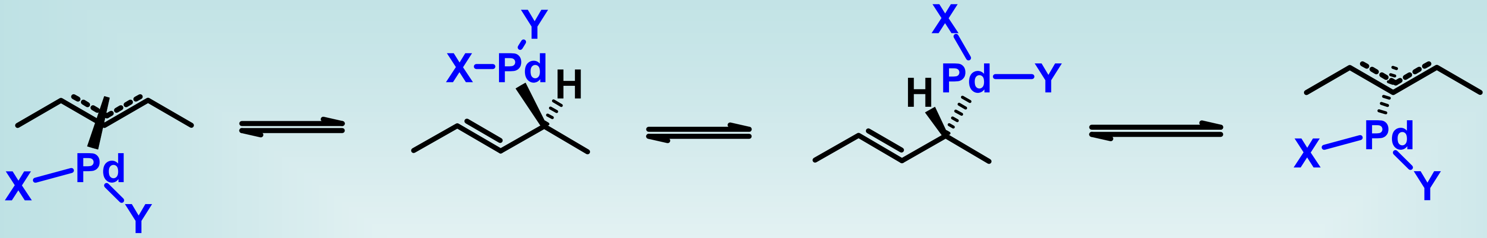
This still can be a very tricky process, as there are many isomerization processes possible



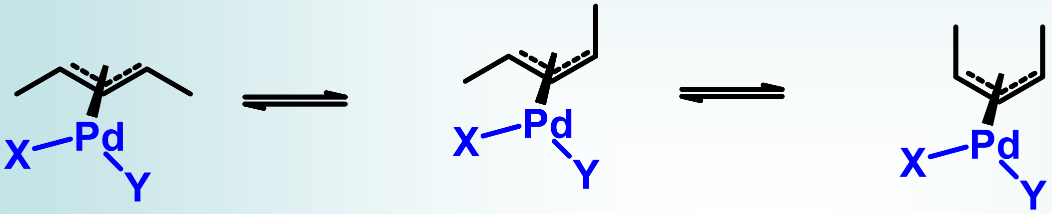
1) Under normal reaction conditions (high phosphine to Pd ratios), nucleophilic displacement is slow relative to π-allyl interconversion

-therefore, the product <u>can</u> depend of <u>stabilities</u> of <u>A</u> and <u>B</u>

2) Acyclic systems can racemize by an η^3 - η^1 - η^3 mechanism

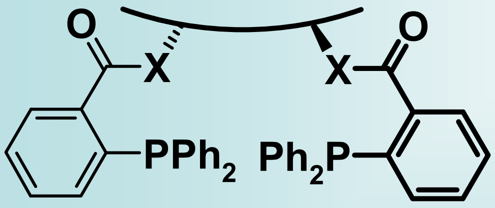


-same process can also result in *anti* / *syn-* isomerization of allyl Pd's



syn,syn- *syn,anti-* *anti,anti-*

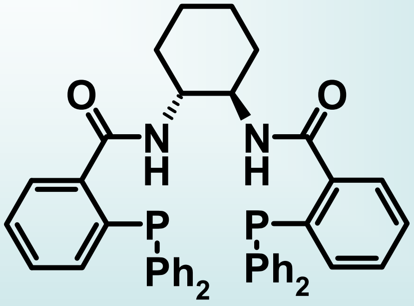
Nevertheless, there has been considerable success in this enantioselective transformation, especially using ......



DPPBA ligands

where

is a symmetrical diol diamine

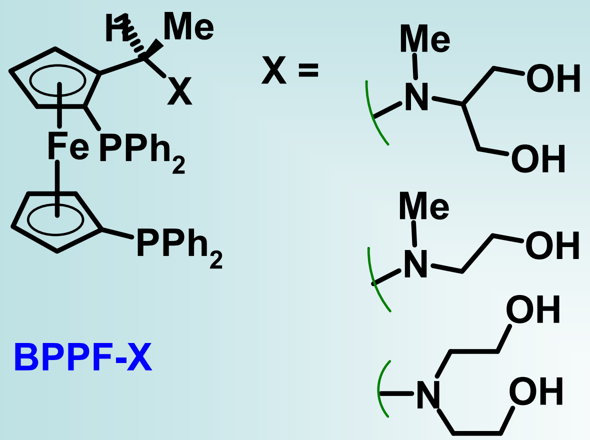


most common

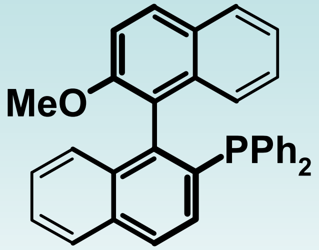
see Trost reviews listed on last page

R Trost. B. M.; Van Vranken, D. L. *Chem. Rev.* 1996, *96*, 395.

Other successful ligands



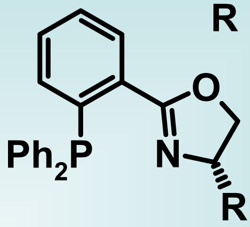
BPPF-X

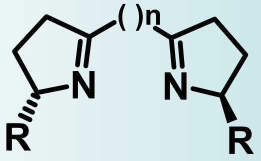


MOP (Monophosphine ligands)

R Hayashi, T. *J. Organomet. Chem.* 1999, *576*, 195.

R = ^{i}Pr, ^{t}Bu



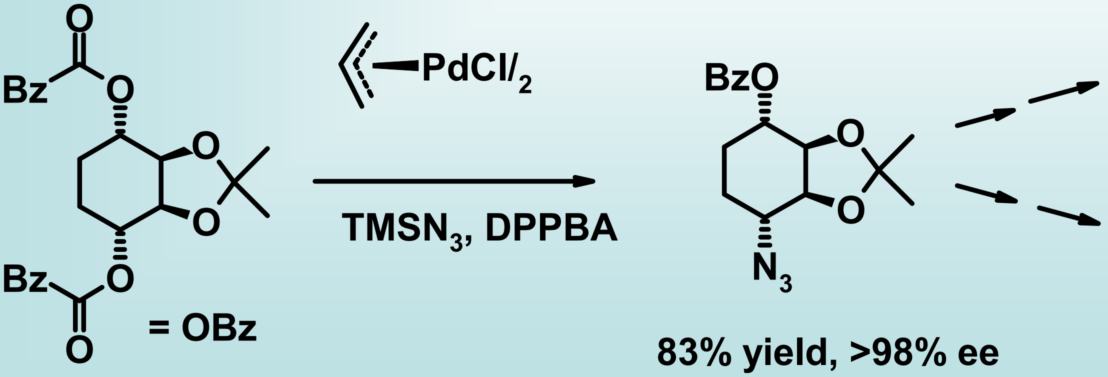


BOX (Bis-oxazoline ligands)

R Pfaltz, A. *Acc. Chem. Res.* 1993, *26*, 339.

up to 96% ee with (R)- or (S)- BPPFX

Hayashi, T. et al *Tetrahedron Lett.* 1986, *27*, 191.



conduramine A-1
benzamide

pancratistatin

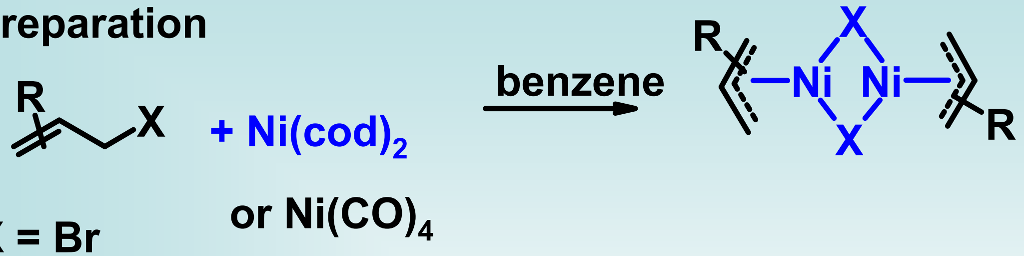
83% yield, >98% ee

from Trost (1996) review

π-Allylnickel Halides

Preparation

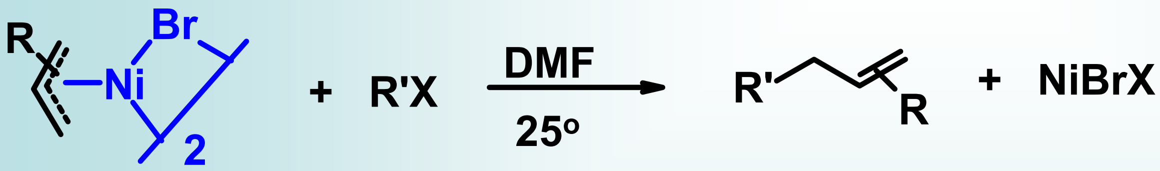
Hegedus, p.278



X = Br
usually

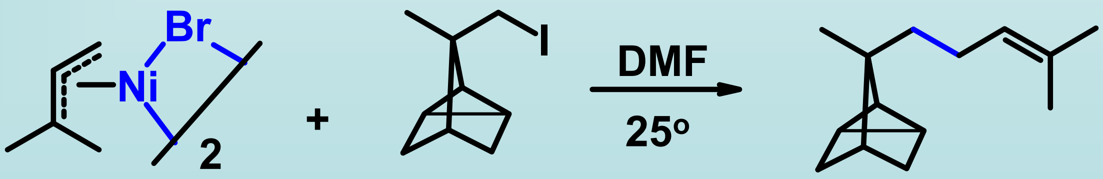
-These are isostructural, isoelectronic with the corresponding allylpalladium compounds
-Reactivity can be different, however

These can behave as if they are <u>nucleophiles</u> themselves, and will allylate organic halides
(X = Br, usually)



-ketones and aldehydes are often tolerated (i.e., they survive this rxn at RT)
-esters are tolerated well

Regiochemistry - reaction occurs at less substituted allyl terminus



α-santelene

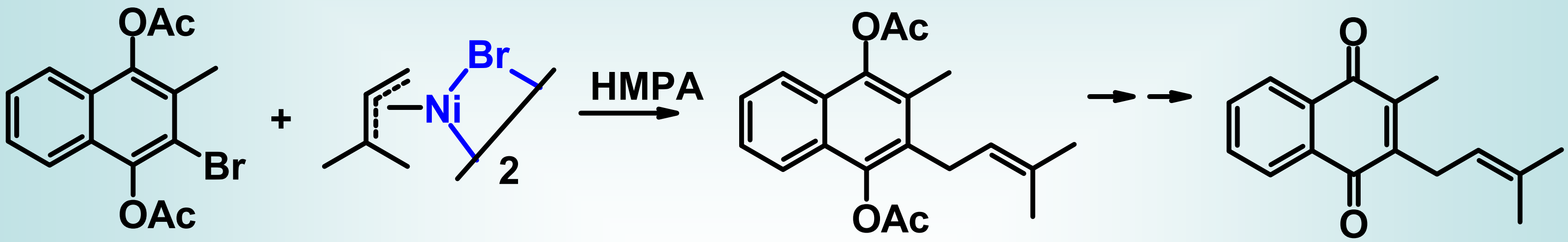
So who cares?

Look carefully at the above; the centre that's being attacked is neopentyl (i.e., $R_3C\text{-}CH_2\text{-}X$)

-neopentyl centres are normally forbidden for nuceophilic (S_N2) substitution

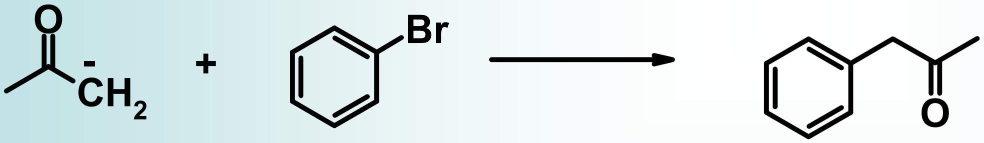
-works just fine here

-Generally true - rxn works well in cases where S_N2 is impossible (i.e., aryl halides)



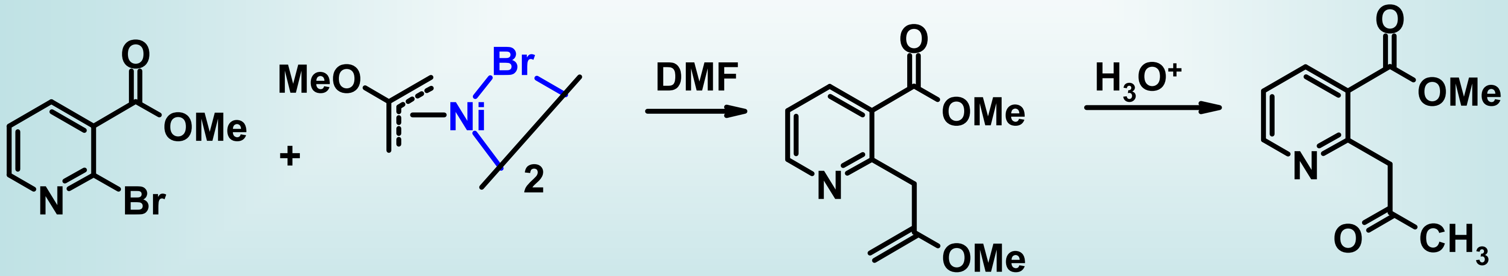
vitamin K analogue

and if you want to do...



-this is very tough directly

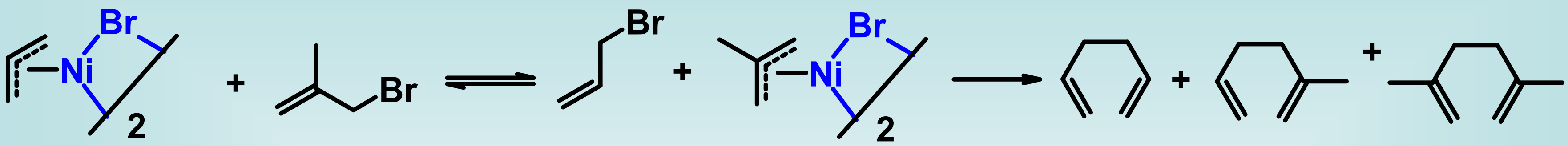
But..



Hegedus, L. S.; Stiverson, R. K. *J. Am. Chem. Soc.* 1974, *96*, 3250.
Hegedus, L. S. et al *J. Org. Chem.* 1977, *42*, 1329.

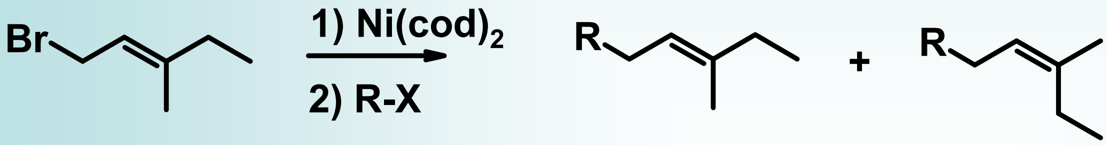
Works with aryl, vinyl, 1°, 2°, 3° alkyl bromides and iodides

However, allyl halides 'scramble'

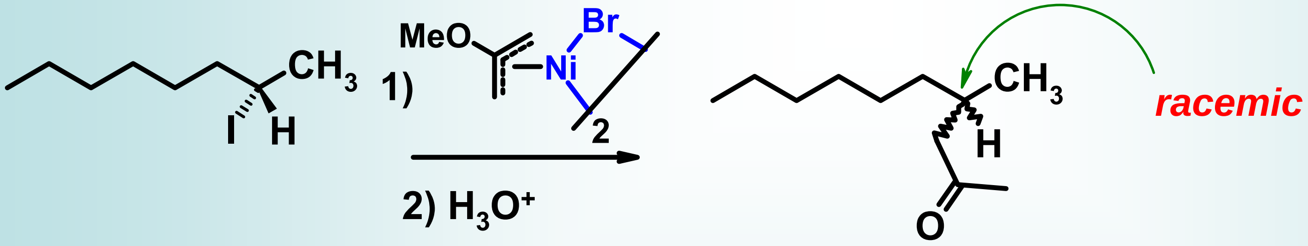


Other points

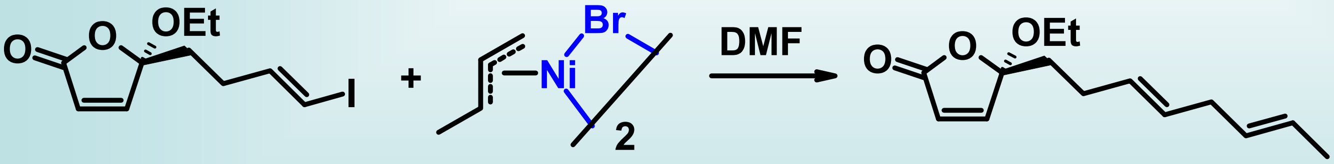
-like allylPd's the allyl fragment loses its stereochemical integrity



-chiral (and enantiomerically pure) 2° alkyl halides ***racemize***



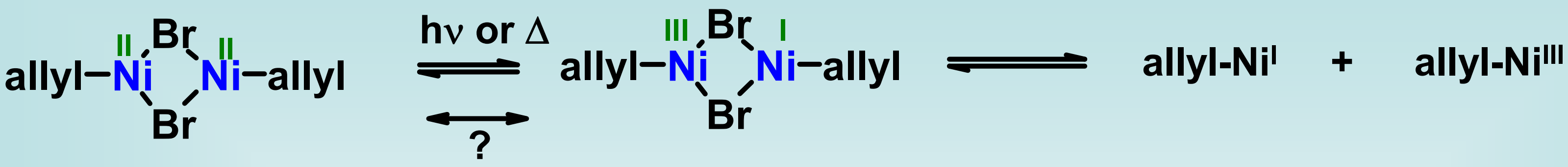
-while vinyl (alkenyl) halides **retain** their stereochemical integrity



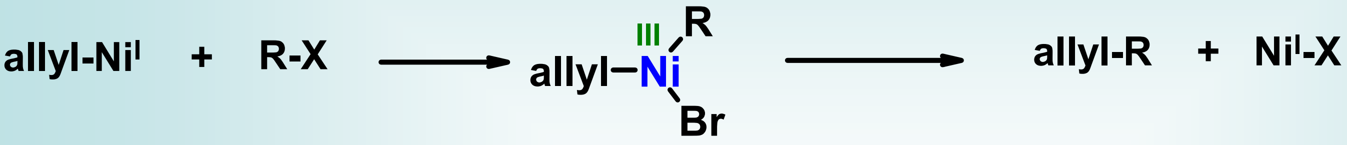
Hegedus believes that this is all due to the interventional of $\mathrm{Ni^{I}}$ and $\mathrm{Ni^{III}}$ as well as $\mathrm{Ni^{II}}$

Hegedus, L. S.; Thompson, D.H.P. *J. Am. Chem. Soc.* 1985, *107*, 5663.

Initiation



Oxidative addition/reductive elimination



Scarmbling of R

Chain carrying step

$$\mathrm{Ni^{I}\text{-}X} \quad + \quad \mathrm{allyl\text{-}Ni^{II}\text{-}Br} \rightleftharpoons \mathrm{Ni^{II}BrX} \quad + \quad \mathrm{allyl\text{-}Ni^{I}}$$

Scrambling of R goes with inversion, i.e., S_N2 like - therefore occurs with alkyls, but not alkenyls

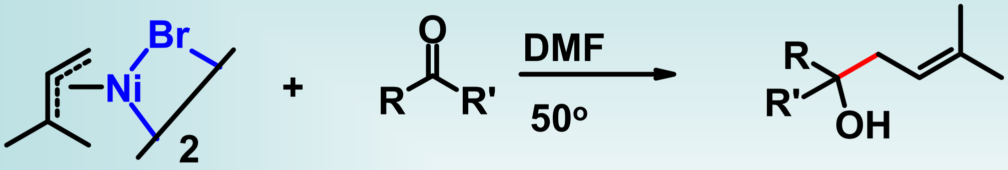
The rest is like you expect - for alkyls, oxidative addition is with inversion, reductive elimination with retention

- for alkenyls, oxidative addition with retention, reductive elimination with retention

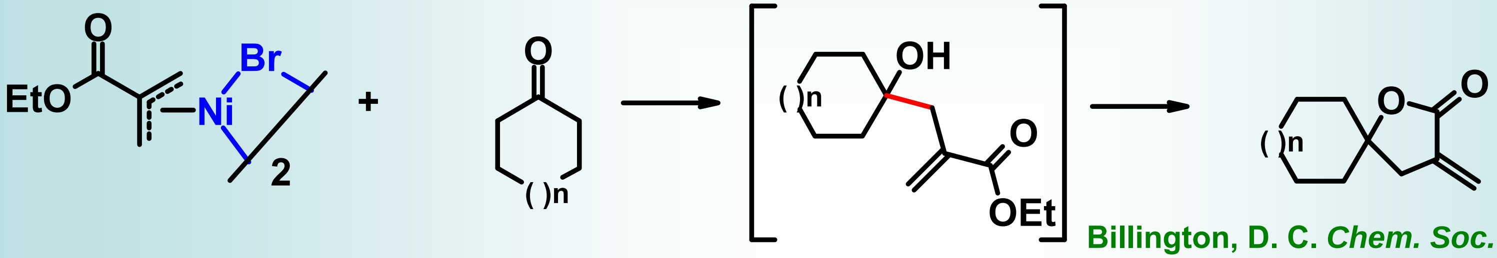
Other electrophiles

-although organic halides react preferentially, these allylnickel species will react with aldehydes and the more reactive ketones at ca. 50°C

-ordinary acyclic aliphatic and α,β-unsaturated ketones only react sluggishly



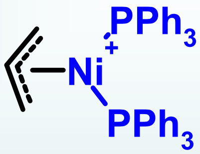
-example of use in spirocyclic α-methylene-γ-butyrolactones



Billington, D. C. *Chem. Soc. Rev.* 1985, *14*, 93.

π-Allylnickels as Electrophiles

With two phosphine ligands



does pretty much the same chemistry as α π-allylpalladium complexes

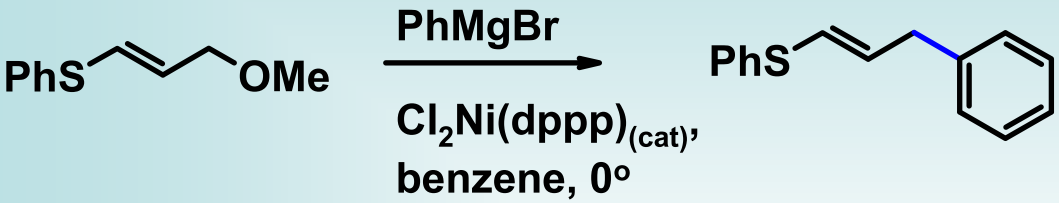
-what's unusual? - successful coupling of Grignard reagents, i.e.,

+ Ni° (or Ni^{II}) + RMgX + 2 PR'$_3$

-large variety of X, including -Br, -Cl, -Oalkyl, -OAr, -OSiR$_3$, -OH, -OTHP, -SR

-the R of RMgX is suprising....R = Ar, or *2° or 1° alkyl*

-β-hydride elimination is apparently a lesser problem in alkyl-Ni β-elimination step for R = alkyls is often slow enough that one can get reasonable amounts of C-C bond formation

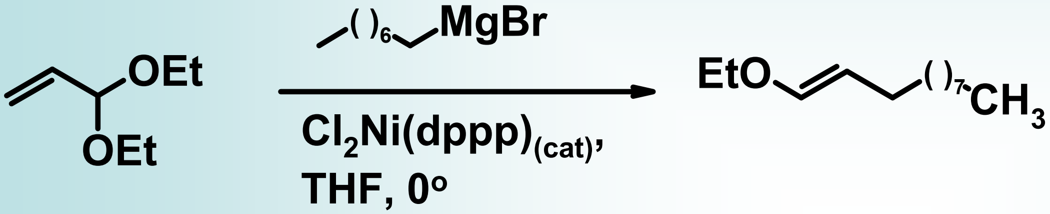


PhMgBr

$Cl_2Ni(dppp)_{(cat)}$, benzene, 0°

95%

Sugimura, H.; Takei, H. *Chem. Lett.* 1984, 351



MgBr

$Cl_2Ni(dppp)_{(cat)}$, THF, 0°

74%

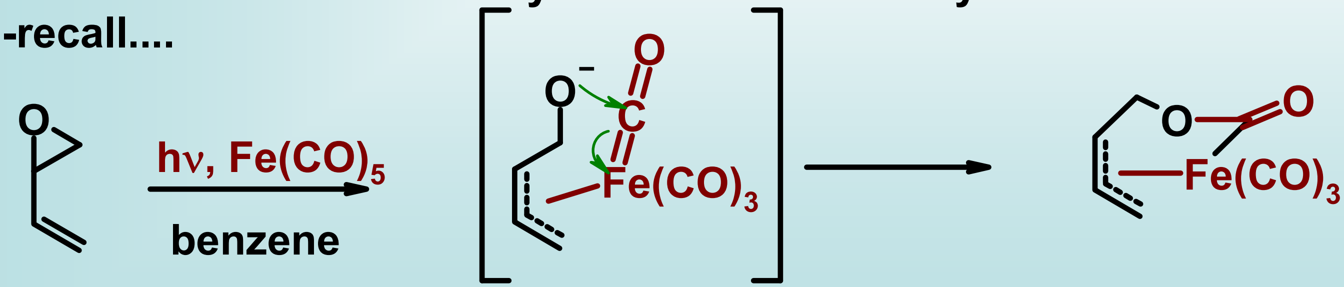
for work with chiral phosphine ligands, see:

Hayashi, T., et al *J. Organomet. Chem.* 1985, *285*, 259.
Cansiglio, G., et al *Tetrahedron* 1986, *42*, 2043.

-Work in this area has slowed drastically since the mid 1980's

π-Allyliron Tetracarbonyl Lactone Complexes

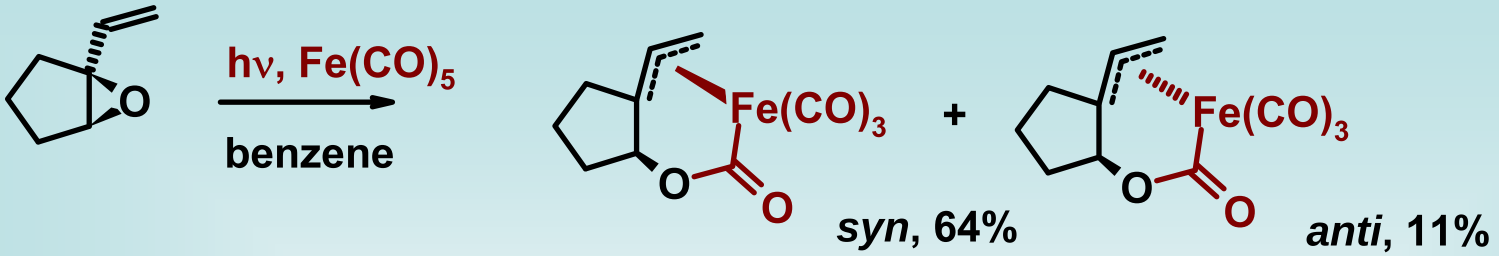
-this area is almost entirely the work of S. V. Ley
-recall....



hν, $Fe(CO)_5$

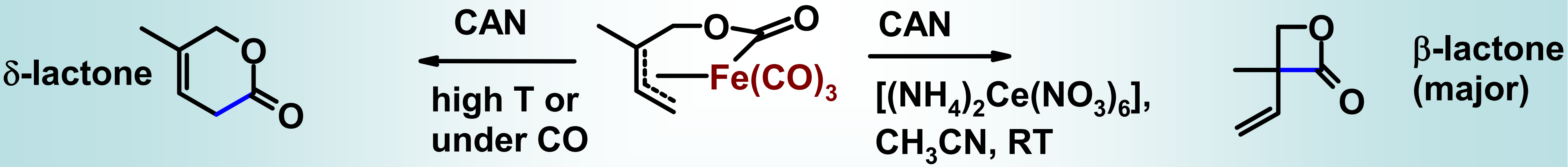
benzene

90%

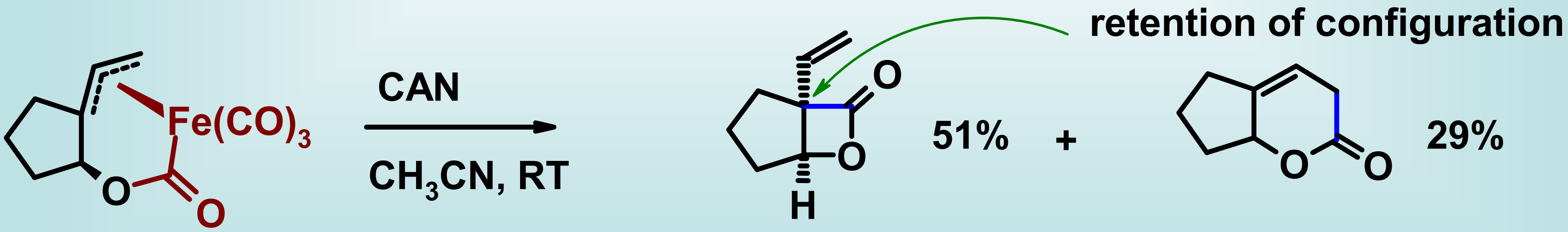


-Note: Photochemical conditions usually give retention (completely) - in above case, one can actually separate the diastereomers chromatographically

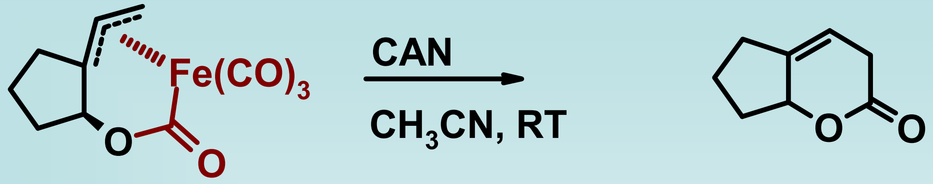
-when one attempts the typical oxidative metallation, it causes *reductive elimination* and therefore C-C bond formation - with two possible outcomes



Note: The stereochemical nature of the reductive elimination step is *retention*

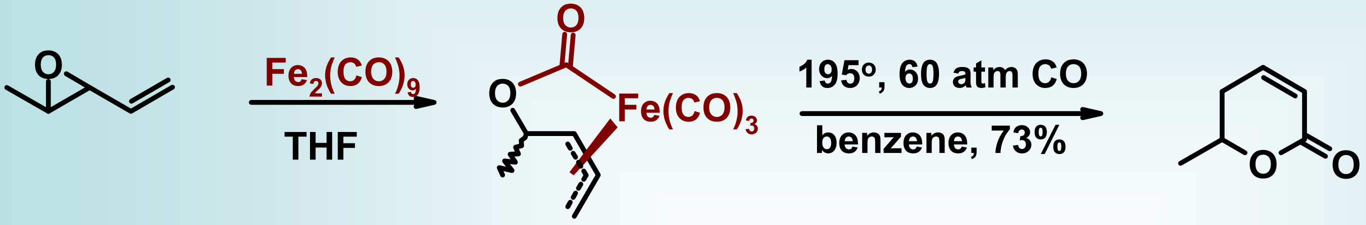


while, conversely

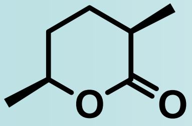


likely because the *trans* fused β-lactone would be impossibly strained

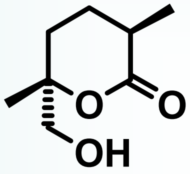
Examples of the use of this in the synthesis of δ-lactones



parasorbic acid lactone (racemic)
-naturally occurring lactone from *sorbus acucupara*



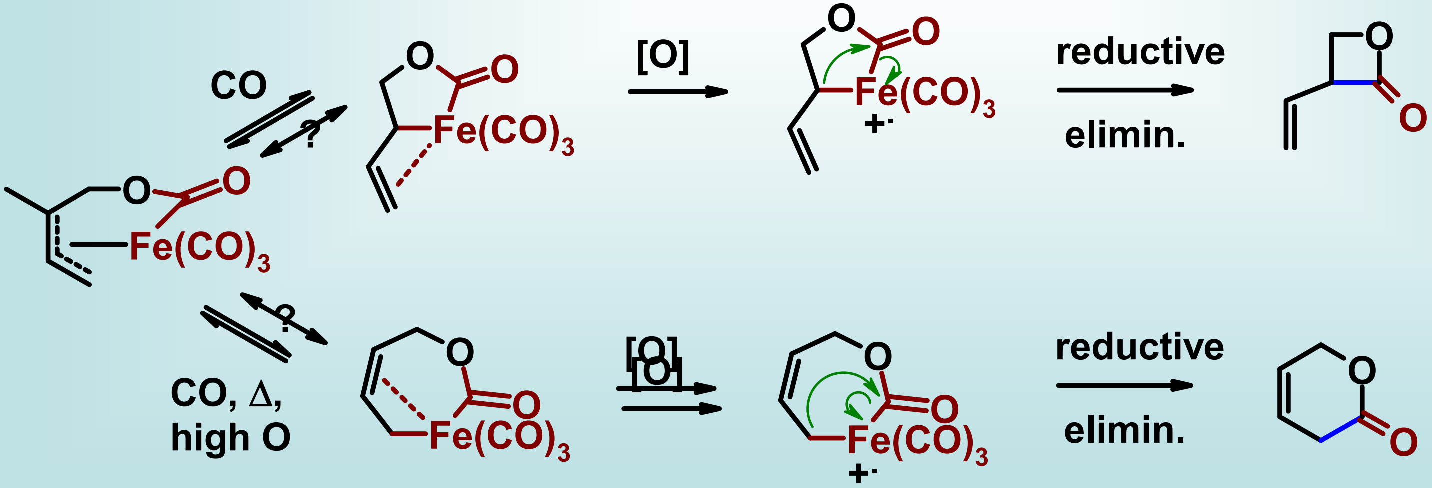
carpenter bee pheromone



malyngolide

Ley, S.V. et al *J. Organomet. Chem.* 1985, *285*, C17.

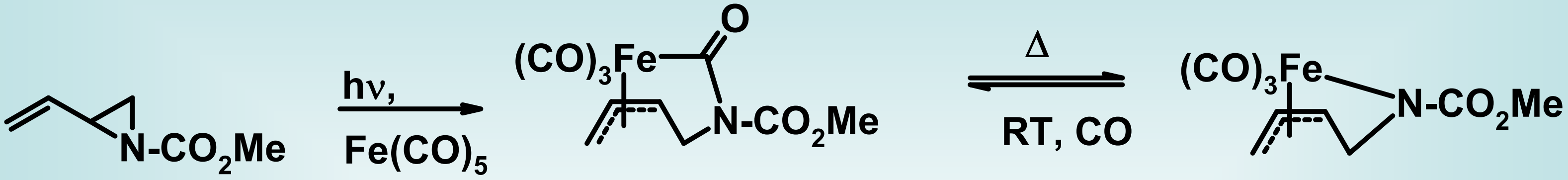
The two routes to C-C brond formation



π-Allyltricarbonyl Lactam Complexes

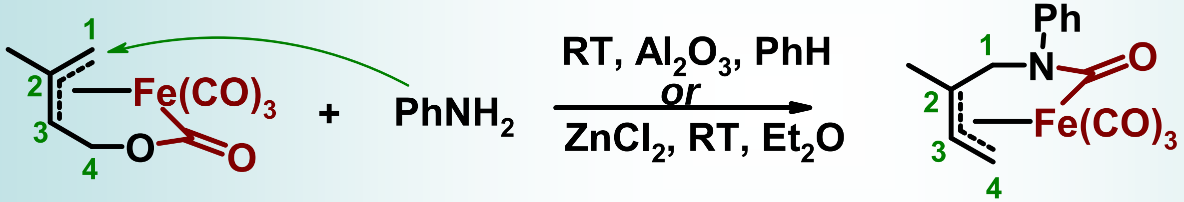
-these have had a larger impact than the corresponding lactone complexes

Preparation - less common

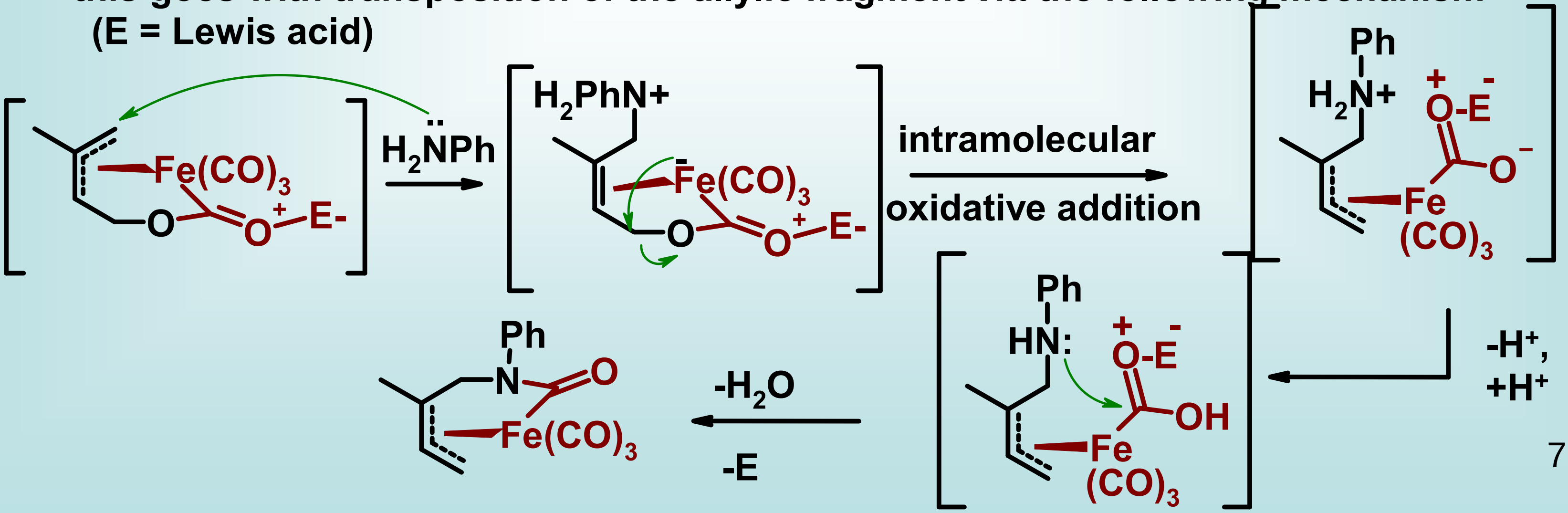


-but, vinyl aziridines aren't all that readily accessible, so....

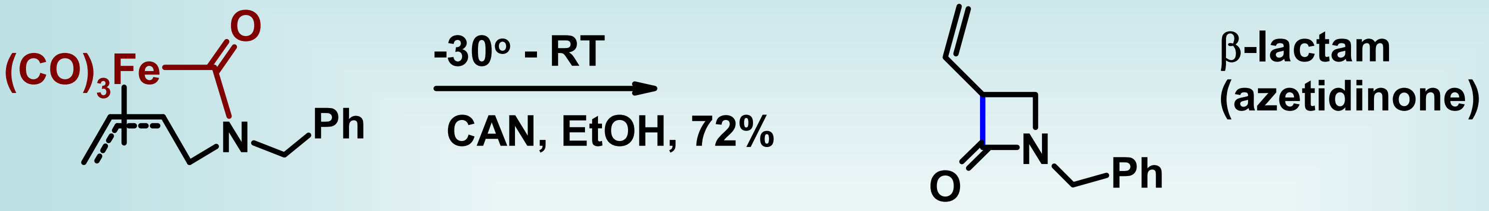
-can be made more readily from the lactone complexes, through Lewis acid mediated substitution



-this goes with transposition of the allylic fragment *via* the following mechanism (E = Lewis acid)

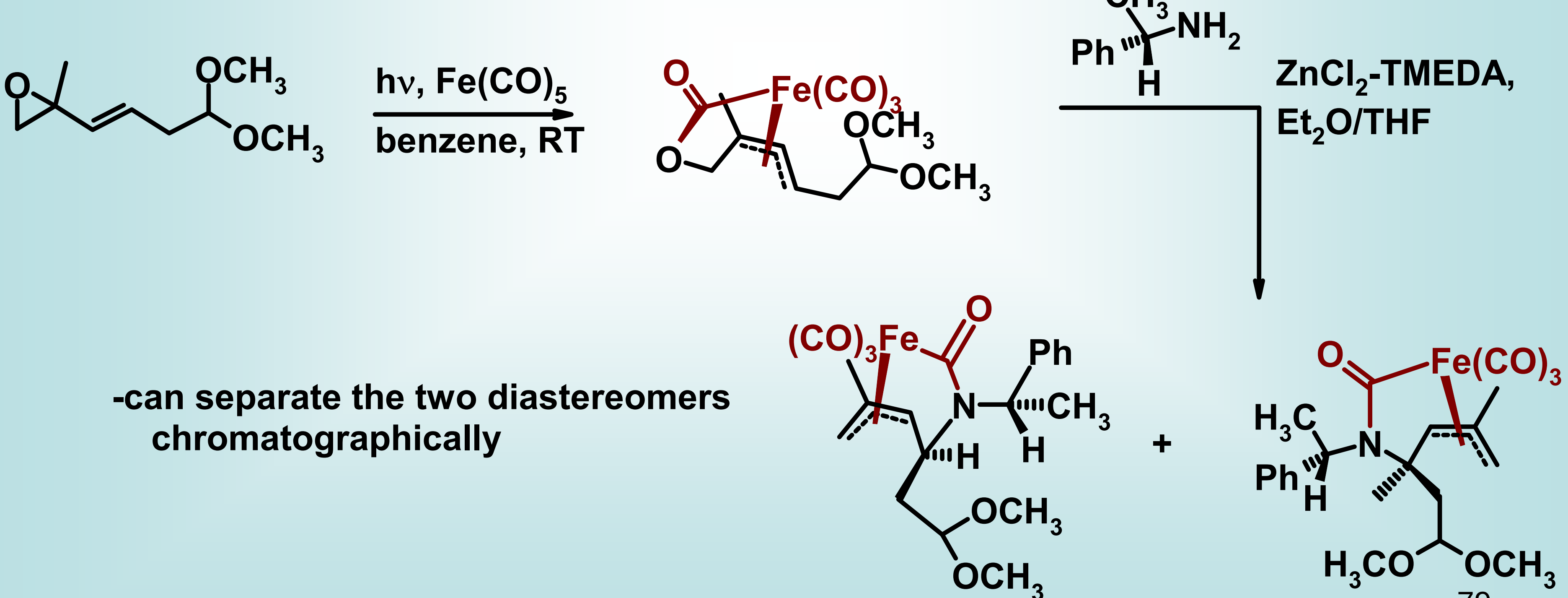


-when these compounds are oxidized, the reductive elimination is more highly selective for the β-lactam

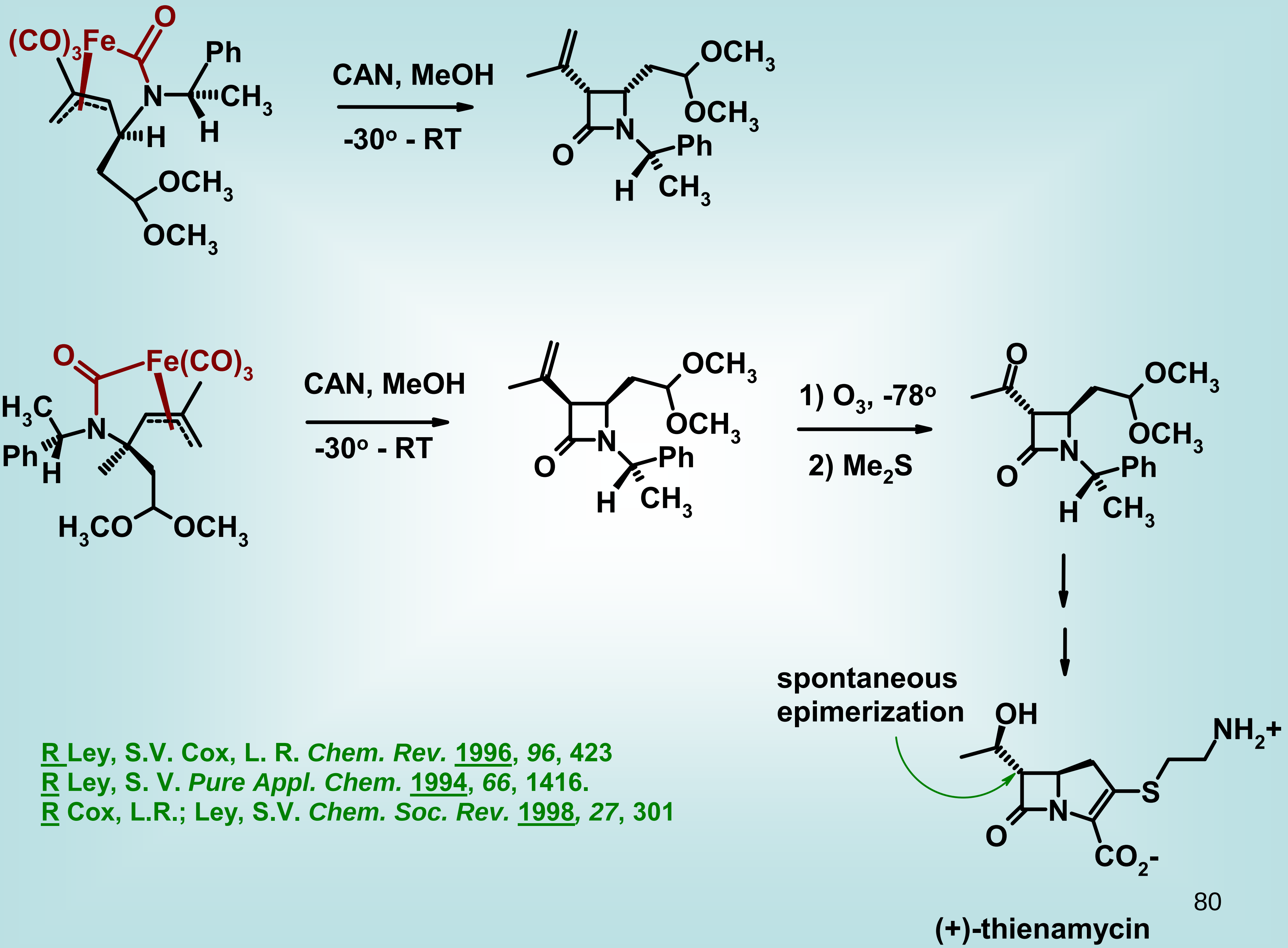


-these 3-alkenyl-2-azetidinones are not so readily accessible for other methods

-example of synthetic use (+)-thienamycin



-can separate the two diastereomers chromatographically



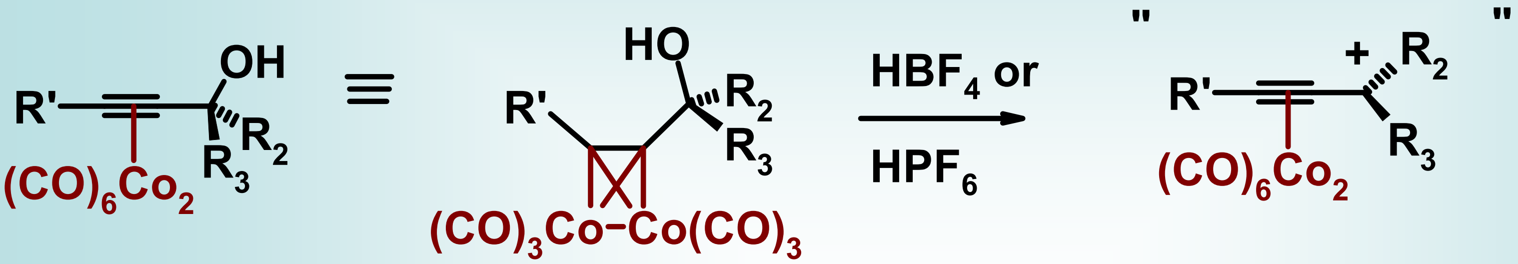
R Ley, S.V. Cox, L. R. *Chem. Rev.* 1996, *96*, 423
R Ley, S. V. *Pure Appl. Chem.* 1994, *66*, 1416.
R Cox, L.R.; Ley, S.V. *Chem. Soc. Rev.* 1998, *27*, 301

Propargyl Cation-Dicobalt Hexacarbonyl Complexes

R Green, J. R. *Curr. Org. Chem.* 2001, *5*, 809.
R Teobald, B. J. *Tetrahedron* 2002, *58*, 4133.

R Caffyn, A.J.M.; Nicholas, K. M. in Comprehensive Organometallic Chemistry II, 1995, V.12, Ch. 7.1
R Nicholas, K. M. *Acc. Chem. Res.* 1987, *20*, 208.

(Di)Cobalt alkyne complexes form cations at the propargylic site very easily



thermally stable, dark red/beet/brown solids

structure is a lie

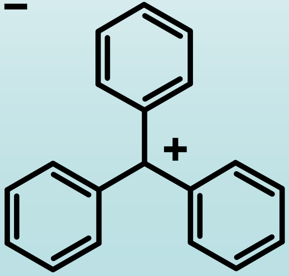
-as cations go, these are very stable
Consider

$$R^+ + 2\,H_2O \overset{K_R+}{\rightleftharpoons} ROH + H_3O^+$$

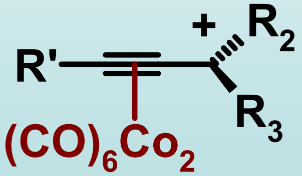
$-\log K_R+ = pK_R+$

i.e., the less negative (more positive) the number, the more stable

Consider Ph_3C^+ =



pK_R^+ = -6.6

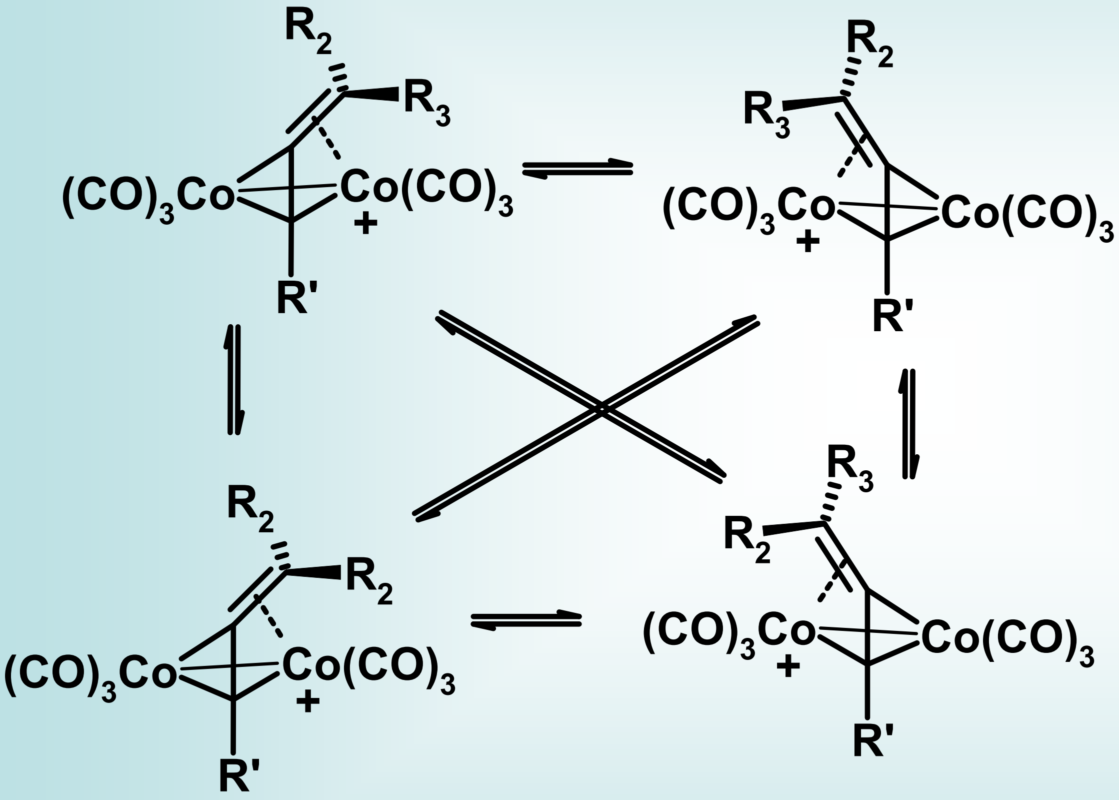


pK_R^+ = -6.8 - -7.4
or -5.5
depending on reference

meaning, about the same

-best estimation of structure Schreiber, S. L.; et al *J. Am. Chem. Soc.* 1987, *109*, 5749.

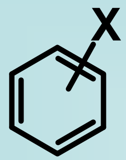
-X-Ray of cation Melikyan, G. G. et al *Angew. Chem. Int. Ed. Engl.* 1998, *37*, 161.



-both antarafacial and supra-facial migrations going on, along with epimerization

-actually pretty complicated

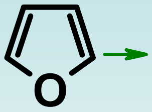
-these are much more electrophilic than allylpalladiums, so they are electrophilic enough to react with several types of nucleophiles

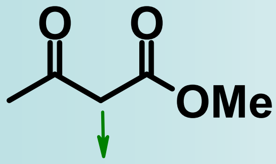


electron rich aromatics

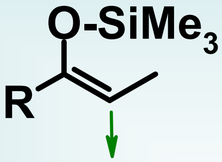
-arene needs one or more activating groups, i.e.,

-OCH_3, -OH, -NMe_2

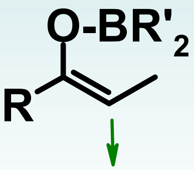




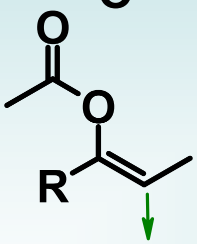
β-dicarbonyls



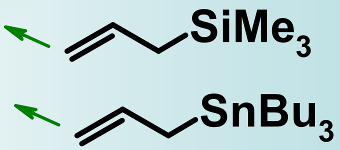
silyl enol ethers
silyl ketene acetals



enol borinates



enol acetates



allylsilanes or allyltins

$NaBH_4$
or
<u>$Et_3SiH + CF_3COOH$</u>

reduction

R_2NH

amines

Et_2AlCN

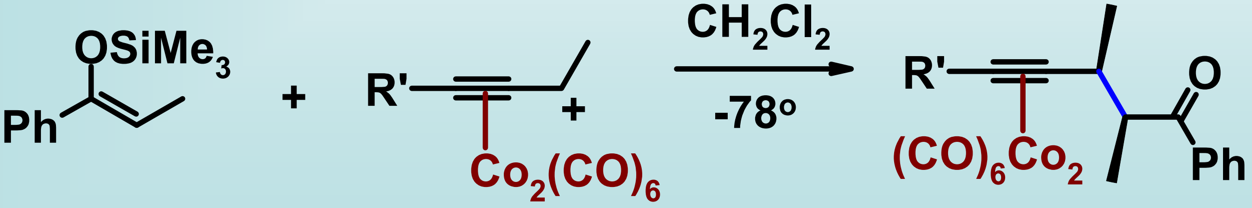
cyanation

R_3Al

alkylation

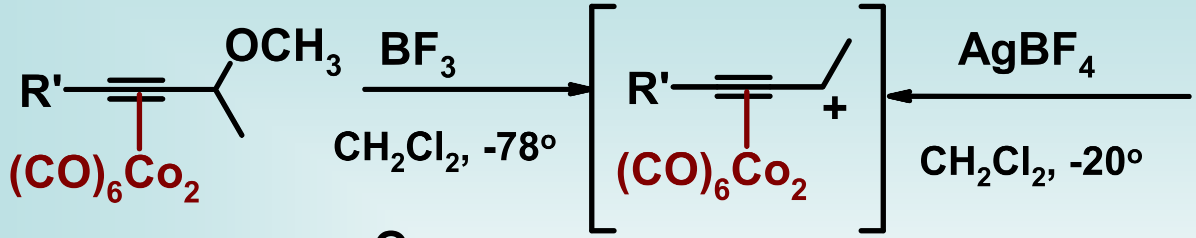
$R_2Cu(CN)ZnI$???

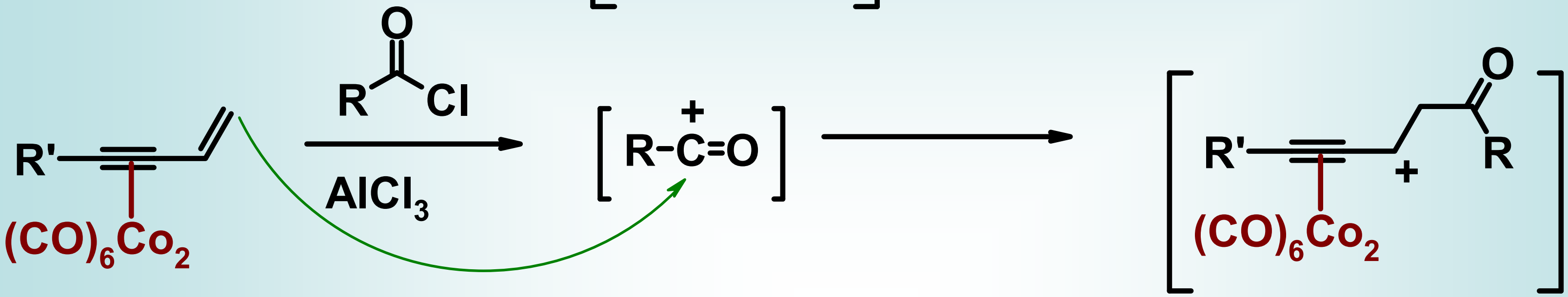
A couple of examples

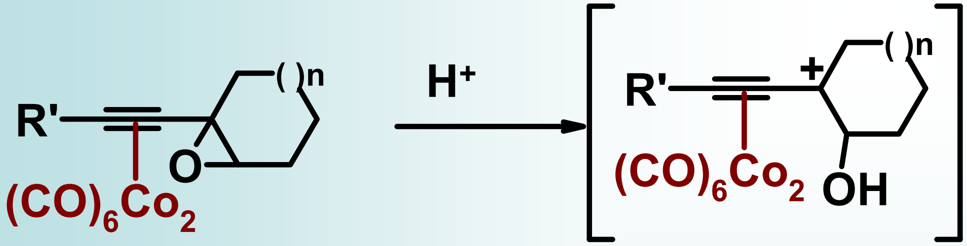


pretty high *syn stereoselection*

-the cations can be generated in several related ways, such as from ethers or acetates, halides, alkenes, epoxides, etc.

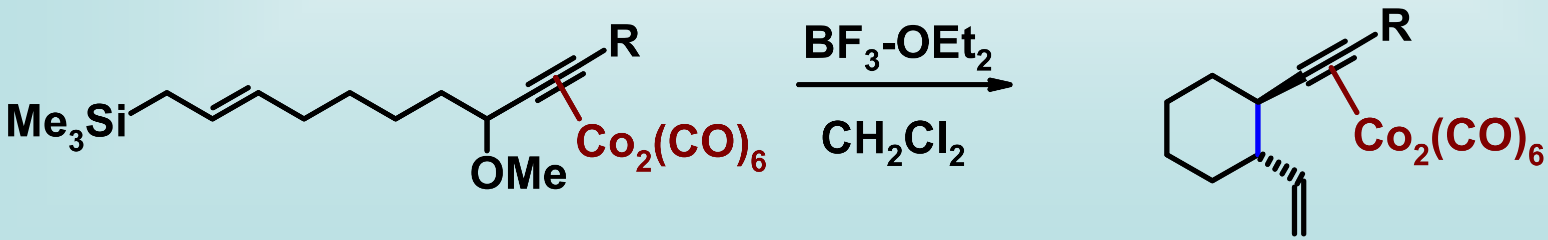


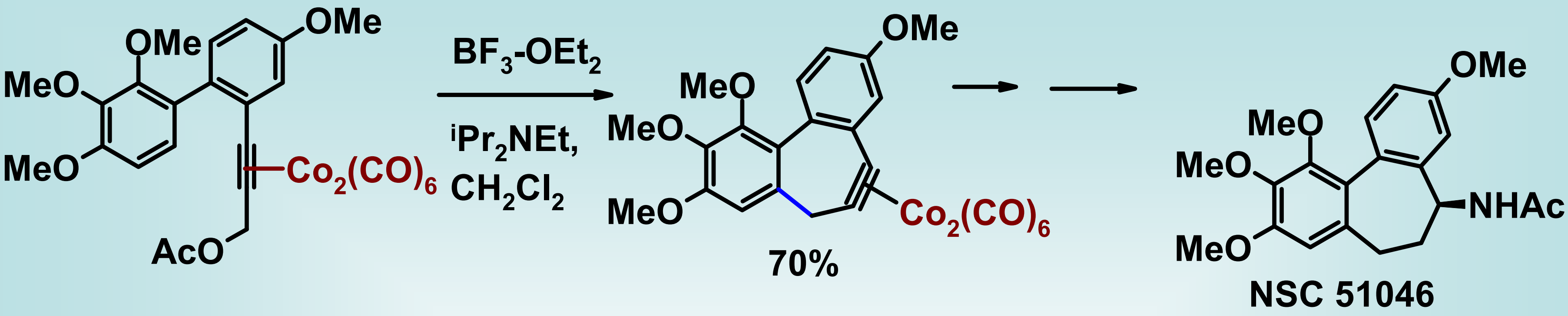




R Smit, W.A.; Caple, R.; Smoliakova, I.P. *Chem. Rev.* 1994, *94*, 2359.

-intramolecular variants of this reation are certainly viable



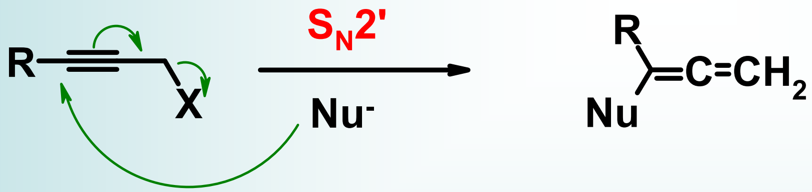


-notice stabilization of 7 membered ring alkyne

in general, the cobalt carbonyl unit can be removed as before (Ce^{+4}, Fe^{+3}, Me_3N^+-O^-)

Importance - in traditional organic chemistry, S_N2' reactions are a major competitive problem in substitutions of propargyl-X

i.e.,

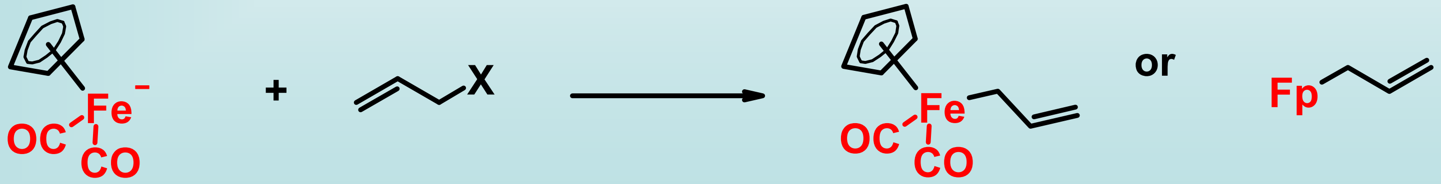


allenes

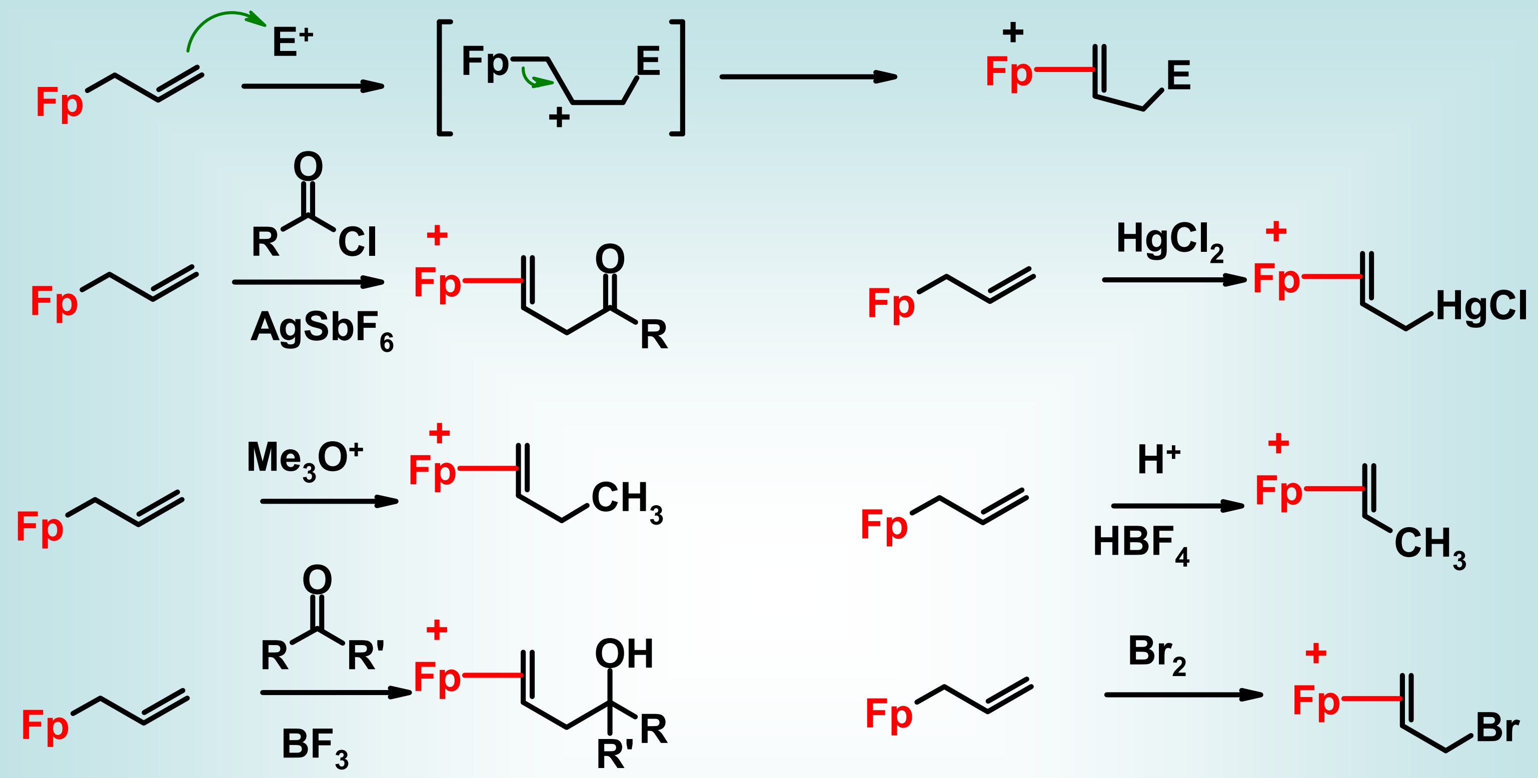
-this never, ever, ever happens with Co propargyl cations (Nicholas reactions)

Other Nucleophilic Allyls

-η^1-allyl Fp [$CpFe(CO)_2$] complexes

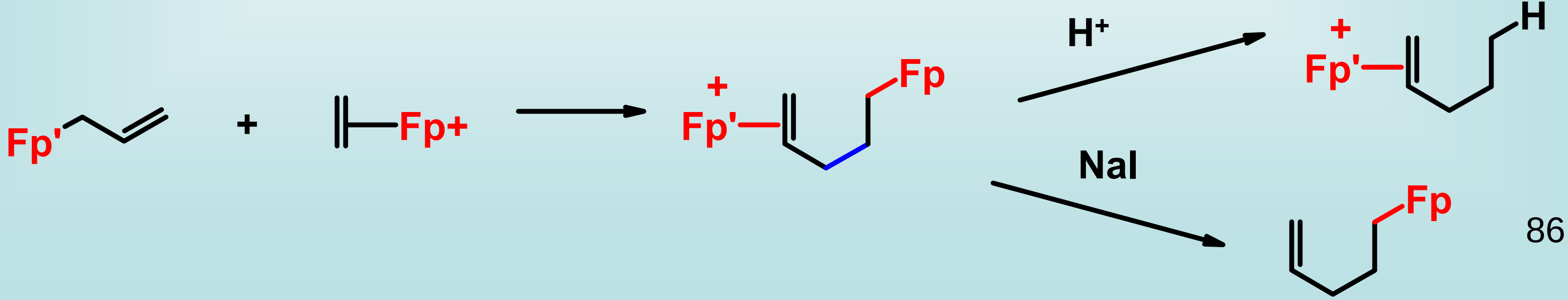


-behave as modestly reactive nucleophiles to a pretty wide range of E^+

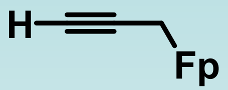


R Rosenblum, M. *J. Organomet. Chem.* 1986, *300*, 191.

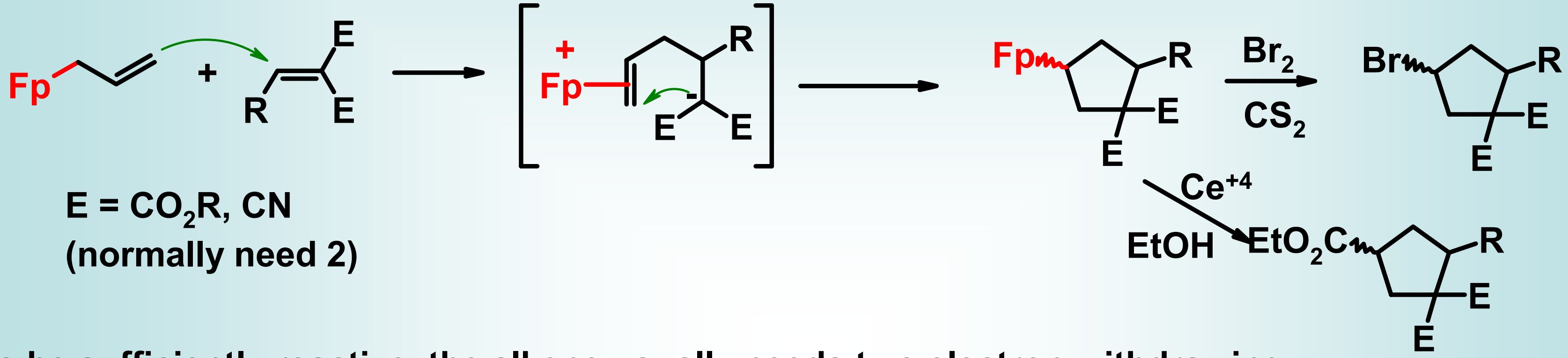
-even Fp^+-alkene complexes will react with these η^1-Fp-allyls



η^1-propargyls do analogous chemistry

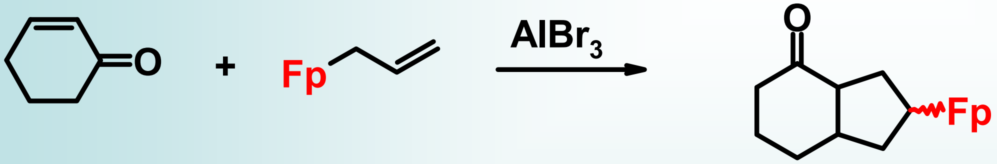


η^1-allyls react with electron poor alkenes by initial nucleophilic attack, followed by electrophilic attack back onto the iron containing unit - this is ultimately a 3+2 cycloaddition resulting



E = CO_2R, CN
(normally need 2)

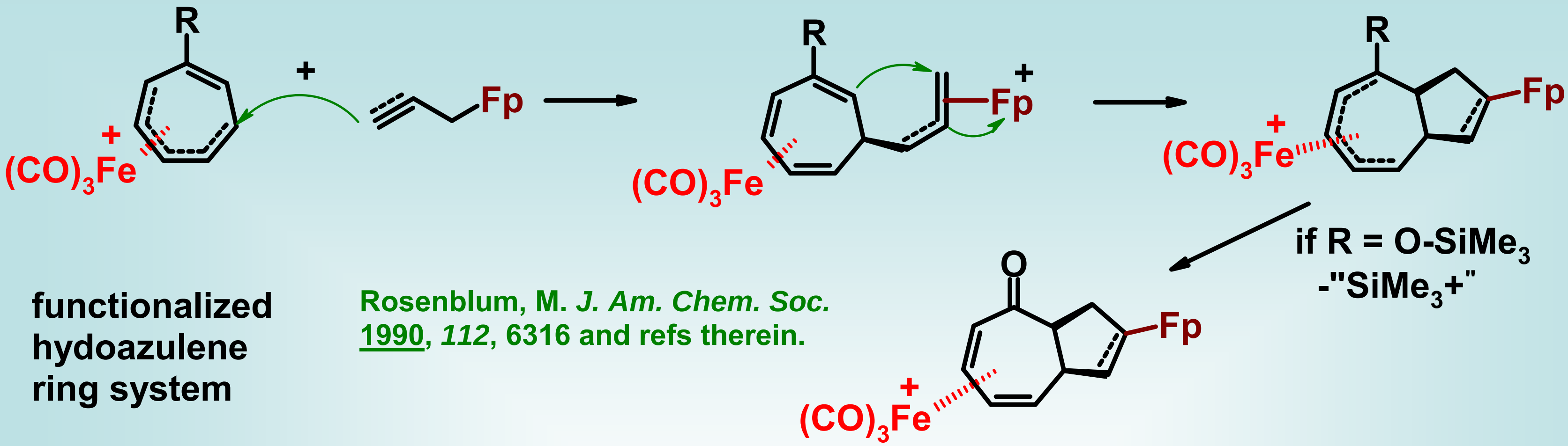
-to be sufficiently reactive, the alkene usually needs two electron withdrawing groups, although some cyclic alkenones work with a Lewis acid added ($AlBr_3$)



-several more obscure electron deficient X=X systems do this [3+2] cycloaddition, but they aren't as important so we'll just list them

$\mathrm{Ts{-}\overset{\delta-}{N}{=}\overset{\delta+}{C}{=}O}$ $\mathrm{MeO_2C{-}\overset{\delta-}{N}{=}\overset{\delta+}{S}O_2}$ $\mathrm{H_2\overset{\delta+}{C}{=}\overset{\delta-}{S}O_2}$

-one further [3+2] cycloaddition partner that is interesting enough to show is specialized; cycloheptadienyl iron cation with an included alkene

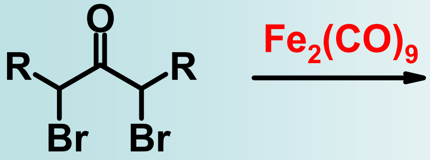


functionalized hydoazulene ring system

Rosenblum, M. *J. Am. Chem. Soc.* 1990, *112*, 6316 and refs therein.

R Ruck-Braun, K.; Mikulas, M/; Amrhein, P. Synthesis 1999, 727.

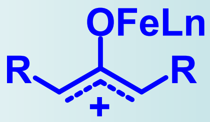
η^3 (?), η^4 (?) Complexes - The Iron Oxyallys



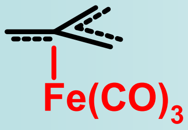
some magical species which has never been isolated

R Noyori, R. *Acc. Chem. Res.* 1979, *12*, 61.
R Noyori, R. *Org. React.* 1983, *29*, 163.
R Mann, J. *Tetrahedron* 1986, *42*, 4611.

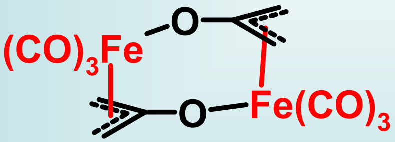
Noyori proposed



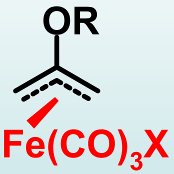
But....the following have been isolated at various times



see later

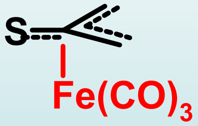


Frey,M.; Jenny *Organometallics* 1990, *9, 1806.*

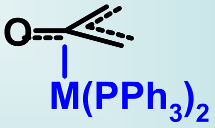


X = Br, Cl
R = H, TMS

J. Organomet. Chem. 1991, *421*, 257.



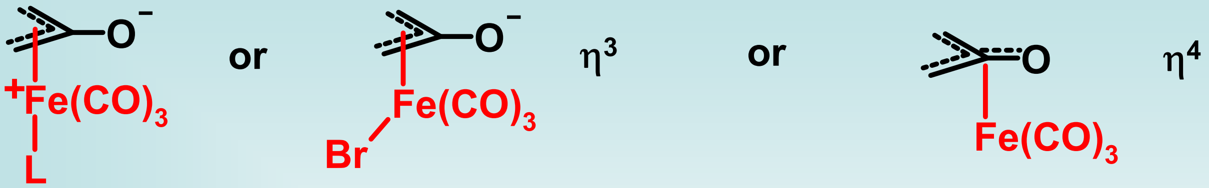
Ando, W. *J. Am. Chem. Soc.* 1990, *112*, 4574.



M = Pd, Pt

Albright, T.A. *Organometallics* 1989, *8*, 199.
Emerson, G.I. *J. Am. Chem. Soc.* 1966, *88*, 3172.

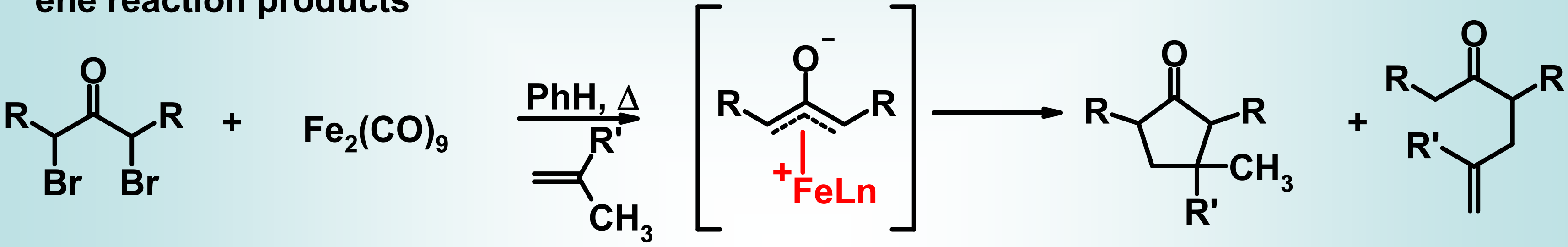
-therefore, the most likely structures for these iron oxyallyls are....



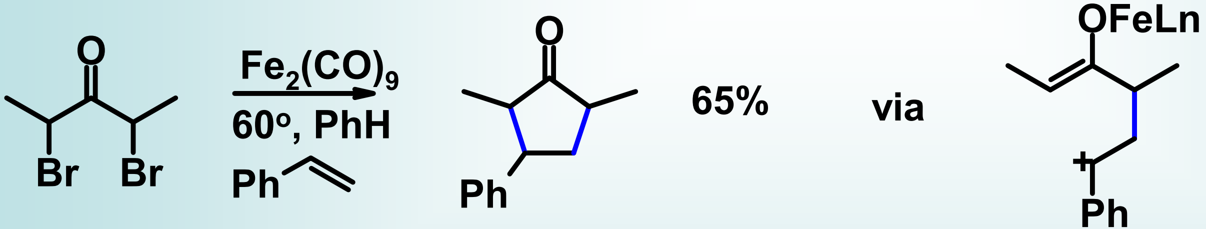
or perhaps a dimer

called oxyallyl cations

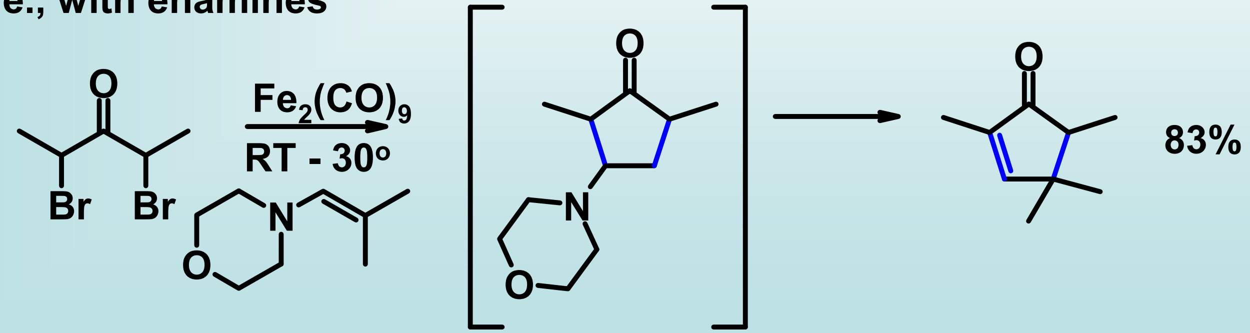
-the iron oxyallys react with simple alkenes to give either [3+2] cycloaddition products or ene reaction products

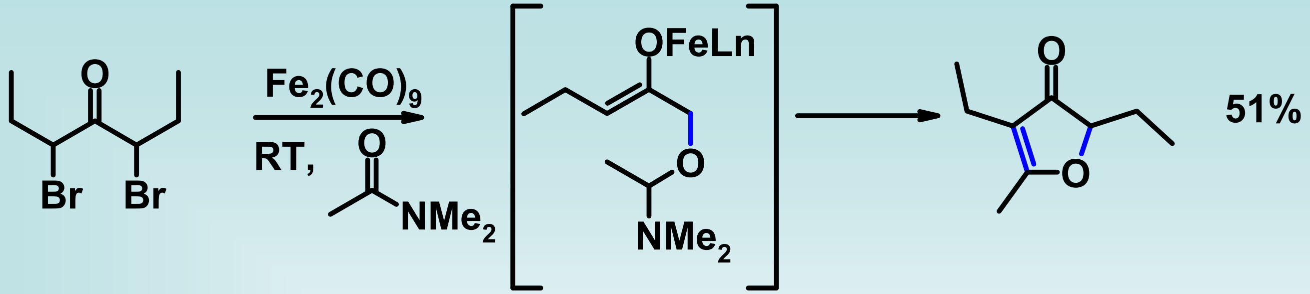


-the [3+2] cycloadditions work best when the alkene has some carbocation stabilizingg groups



-i.e., with enamines



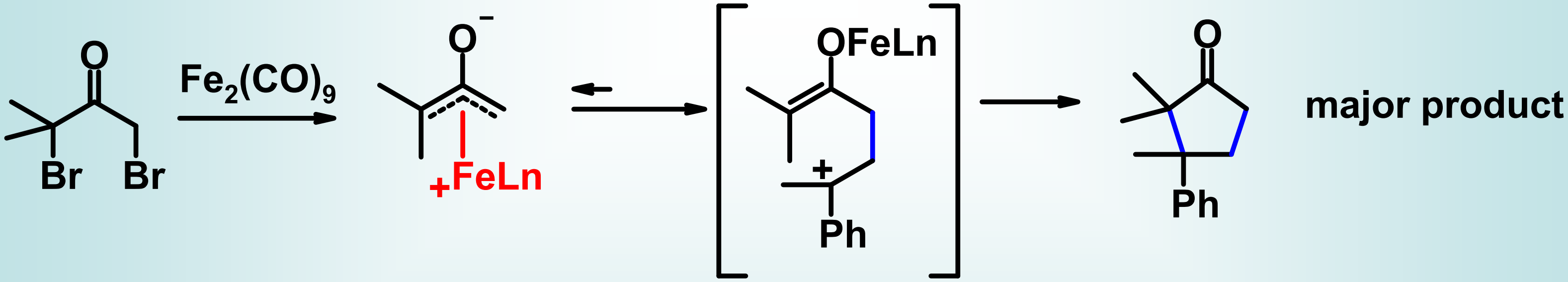


-nitriles also react in a few cases

Regiochemistry

-on the oxyallyl - the major product results from initial reaction at the least substituted end of the allyl (to give the most substituted Fe enolate)

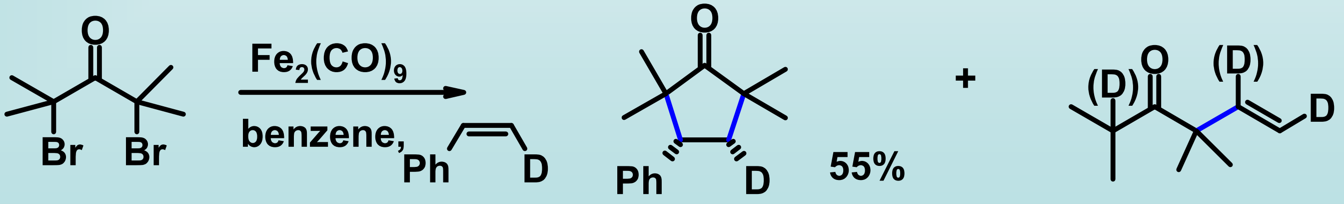
-on the alkene - the major product is the one that goes through the most stable carbocationic intermediate



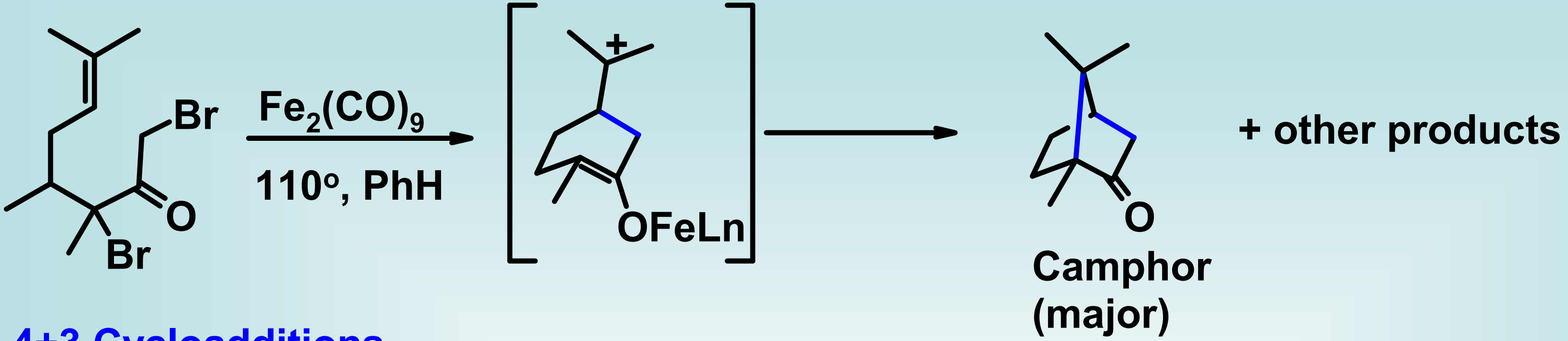
Stereochemistry - normally, one gets retention of stereochemistry about the alkene

-does not mean concertedness; apparently, the intermediate cation is (very) short-lived

-not enough time for bond rotation

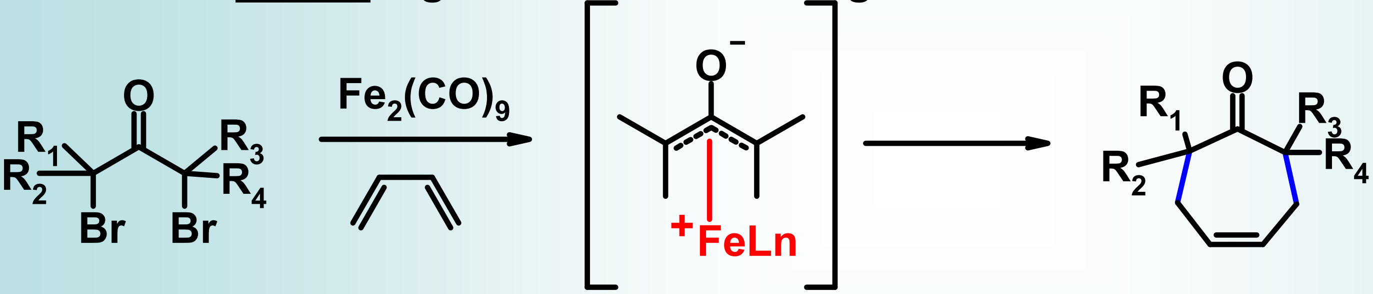


-reaction is certainly not restricted to intermolecular cases; intramolecular ones work as well

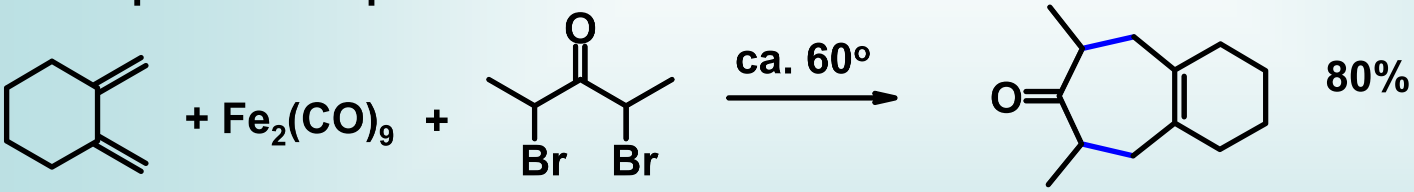


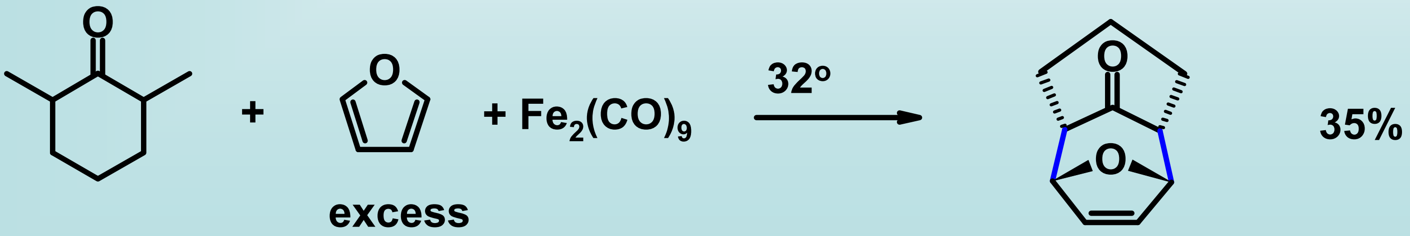
4+3 Cycloadditions

-probably more imortantly than the [3+2] cycloadditions, these oxyallyl cations react with <u>dienes</u> ti give 7- membered rings

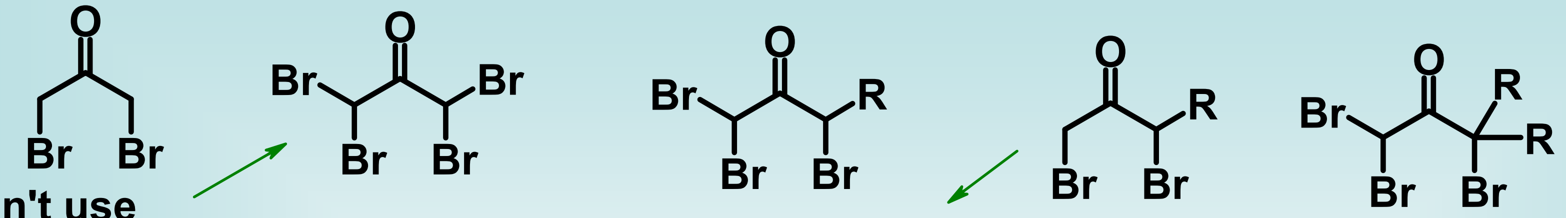


-a couple of examples





Limitations on Reagents in [4+3] - on the dibromoalkene



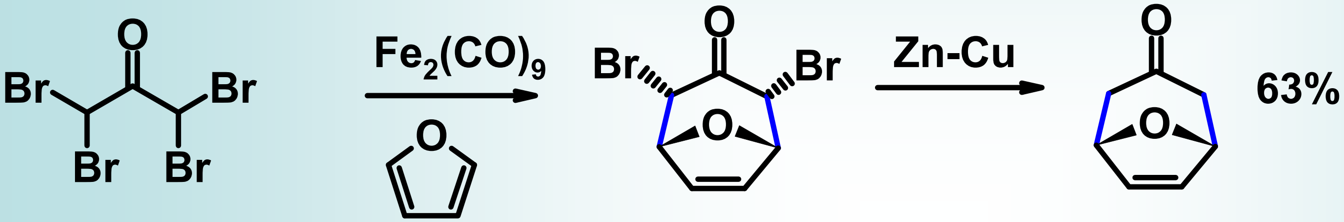
can't use unsubstituted one

used instead

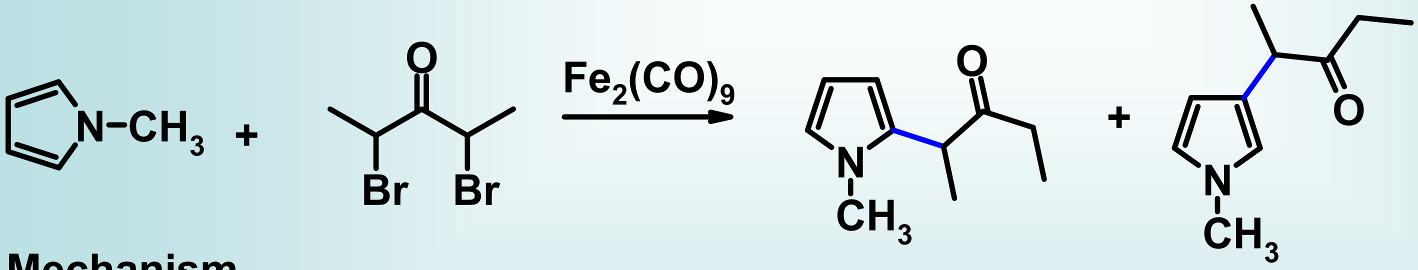
tribromo used instead of....

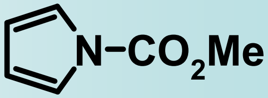
(except R = Ph)

is even used sometimes



-in cases with pyrroles, N-alkyl cases give electrophilic aromatic substitution
N-acyl cases usually give the [4+3]





works, though

Mechanism

-allyl cation is a 3C, 2π electron system; diene is a 4π electron system
-could this be a concerted [4π + 2π] cycloaddition?

-Noyori thinks <u>yes</u>
-Hoffmann thinks only sometimes, but mostly <u>no</u>

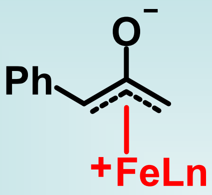
(Angew. Chem. Int. Ed. Engl. 1984, 23, 1)

Regiochemistry

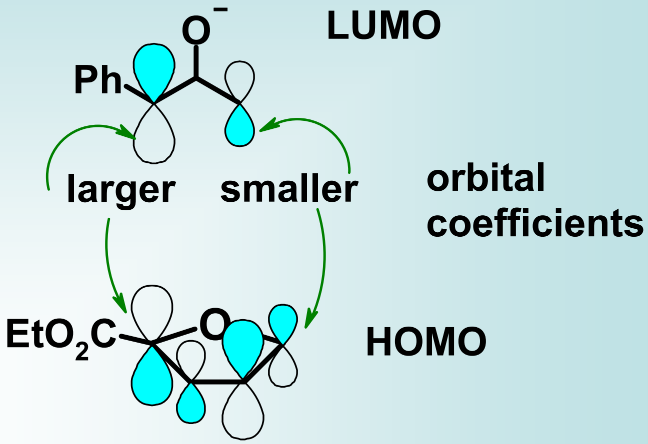
-behaves as if it is a concerted reaction

-therefore, it is controlled by HOMO-LUMO interactions

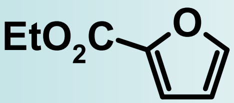
Consider



if we leave out the iron

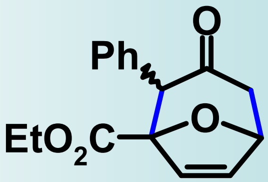


and

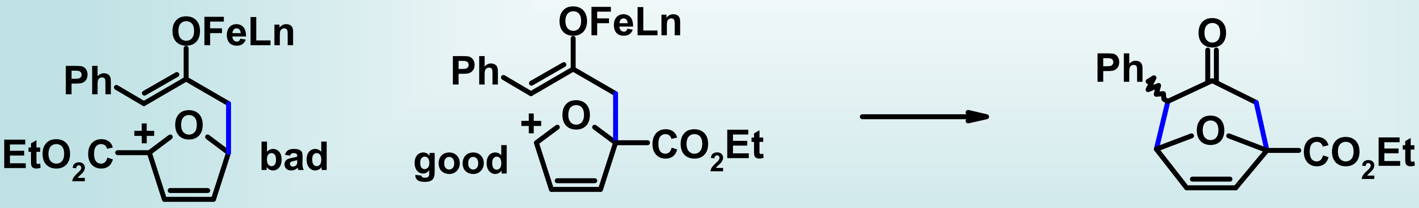


-frontier molecular orbital arguments require that atoms with larger orbital coefficients, and smaller with smaller

-therefore, frontier molecular orbital (FMO) arguments would predict

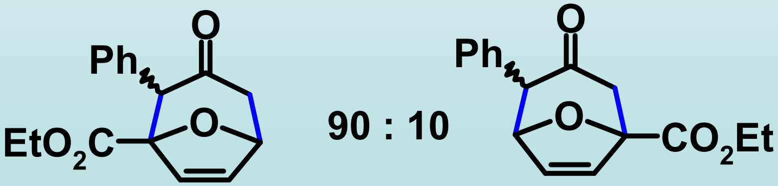


-but if stepwise, one would predict....



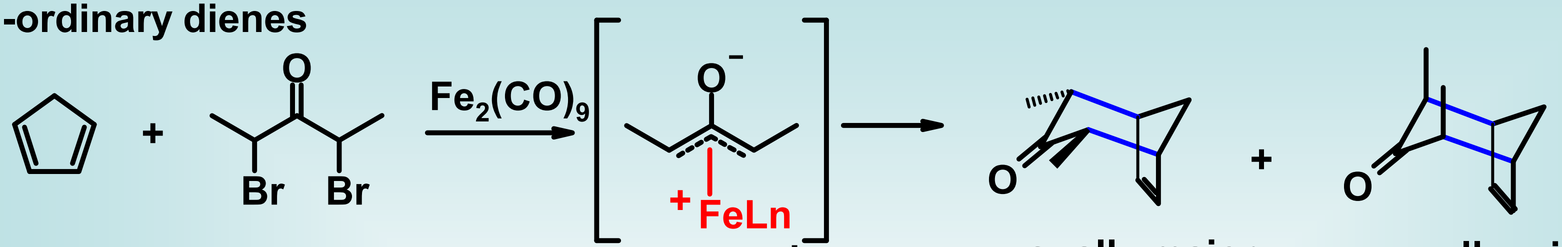
would be favoured

-the actual result is....



Stereochemical consequences

-ordinary dienes

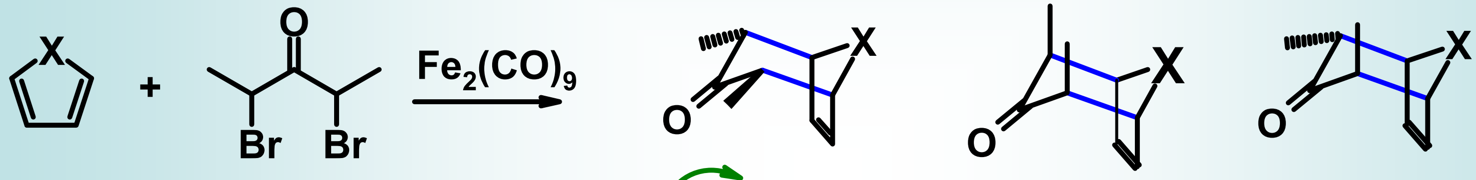


presumed configuration

usually major (endo)

usually minor (exo)

-aromatic dienes



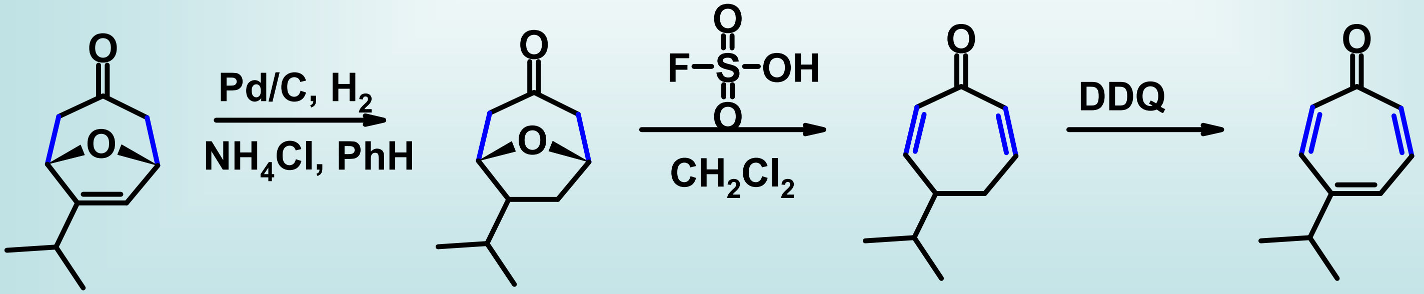
X = O, N-EWG

pretty much a random mixture

-it is the presence of these types of products that makes Hoffmann think that the reaction is not concerted

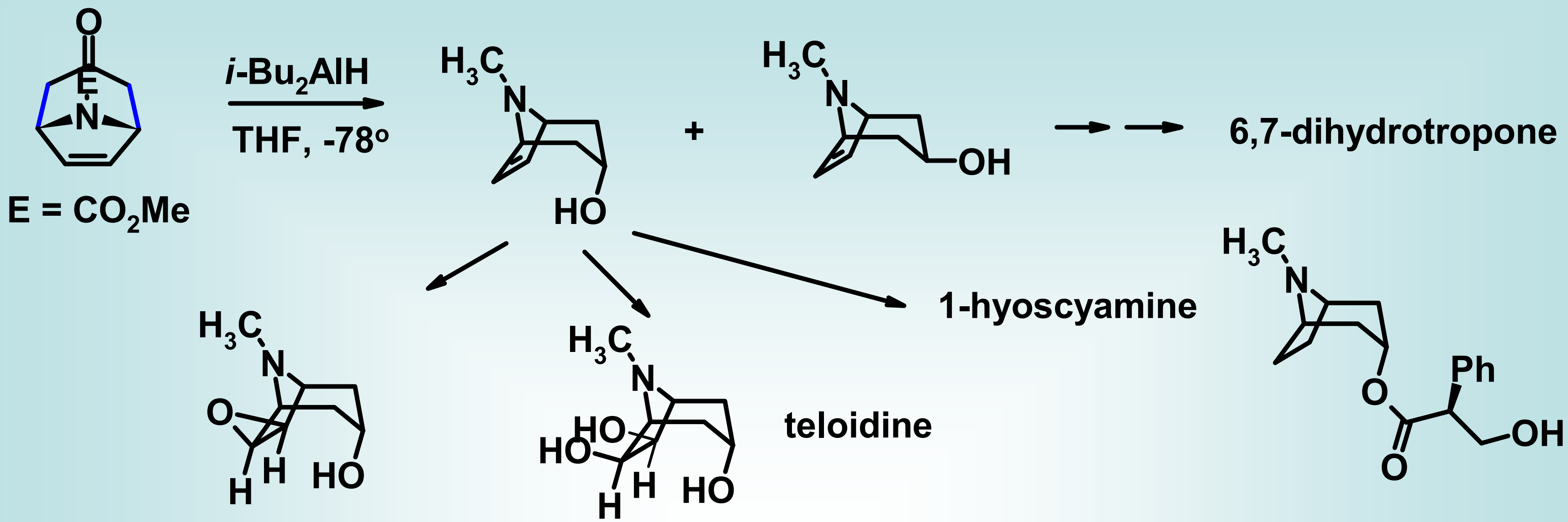
-use - pretty good way of making 7-membered ring containing natural products

i.e.,



nezukone

-also, in tropane alkaloid synthesis...



many other natural product syntheses

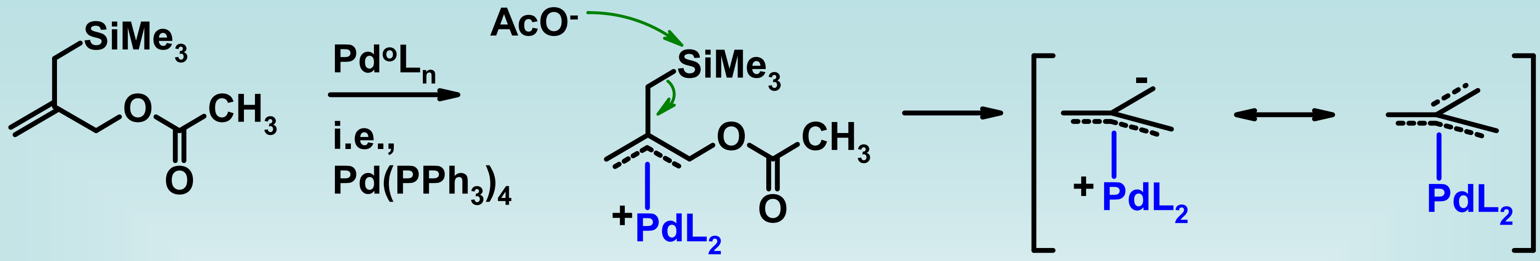
for reviews, see R Noyori, R. *Acc. Chem. Res.* 1979, *12*, 61.
R Noyori, R. *Org. React.* 1983, *29*, 162.
R Mann, J. *Tetrahedron* 1986, *42*, 4611.
part of R Rigby, J. H. Pigge, F. C. *Org. React*. 1997, *51*, 351
R Harmata, M. *Tetrahedron* 1997, *53*, 6235

η^4- Complexes

η^4-Trimethylenemethane Complexes

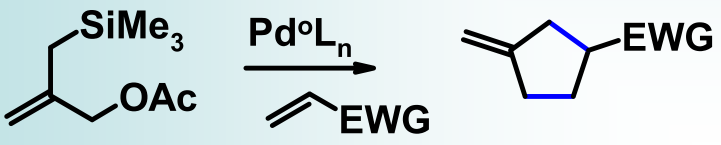
-predominantly used with palladium, due to use of metal in catalytic amounts
 -iron also known and used some, but it is stoichiometric

-consider the following substrate that looks like a precursor to an η^3-allylpalladium

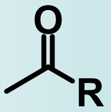


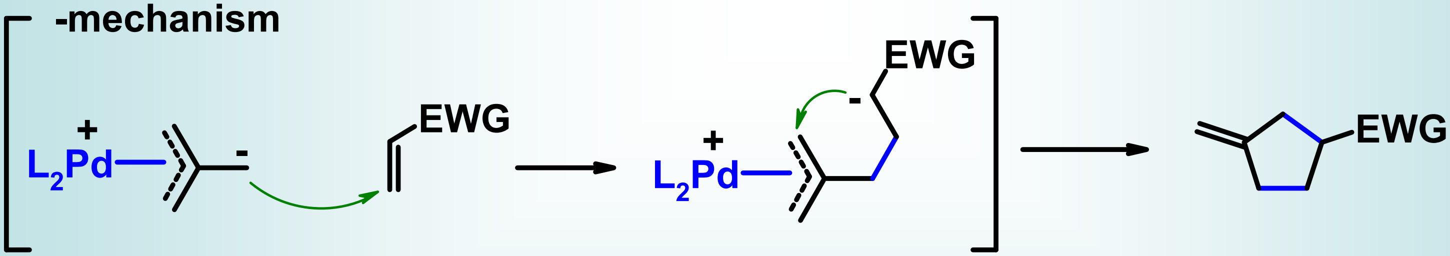
- in these cases, the Pd is coordinated to all 4 carbon atoms
- this is a <u>trimethylenemethane</u> complex

-excellent reagent for 3+2 cycloaddition reactions



EWG = -CO_2R, -CN, -SO_2R,

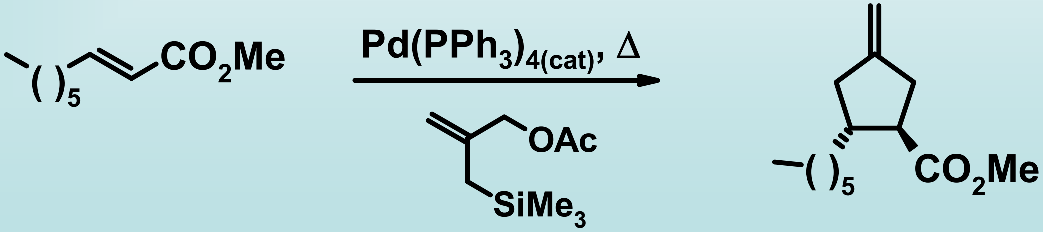


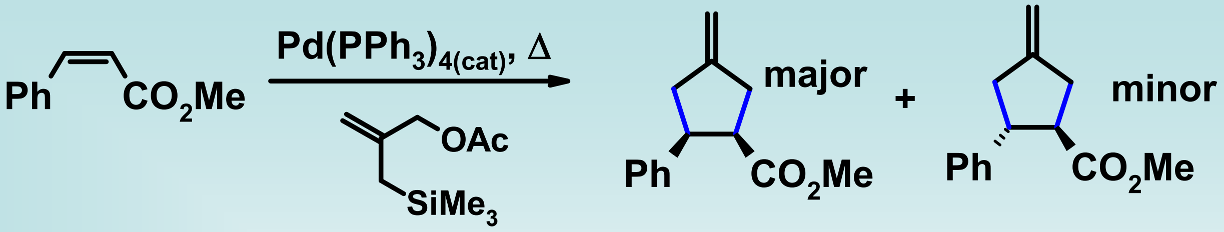


-mechanism

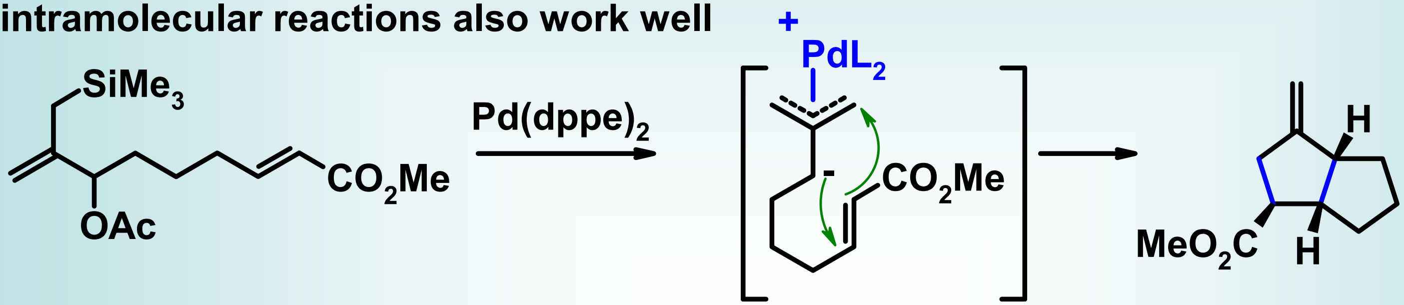
-stereochemical considerations

-about alkene - get mostly retention of configuration, but not <u>perfectly</u> so



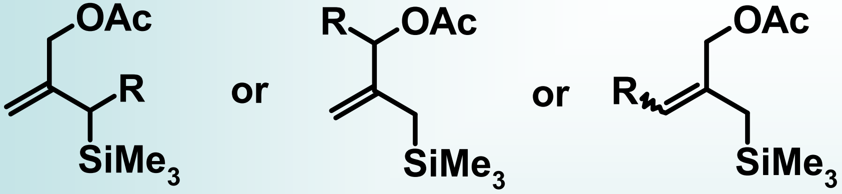


-intramolecular reactions also work well



-other aspects of the stereochemistry (i.e., diastereoselectivity) have been well established, but are beyond the course's scope

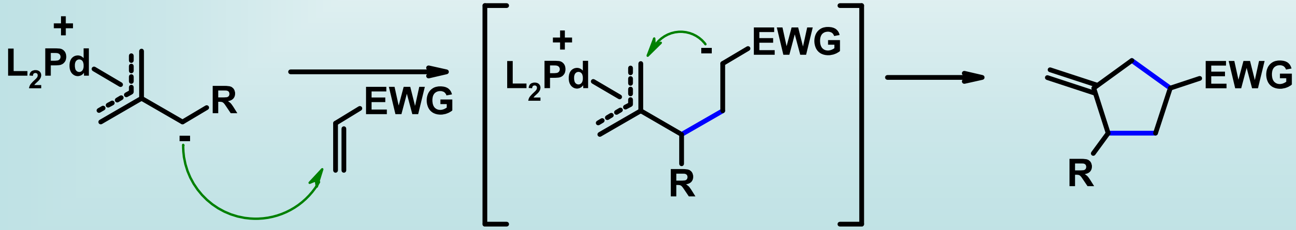
Regiochemistry



R = alkyl
electron withdrawing
electron donating

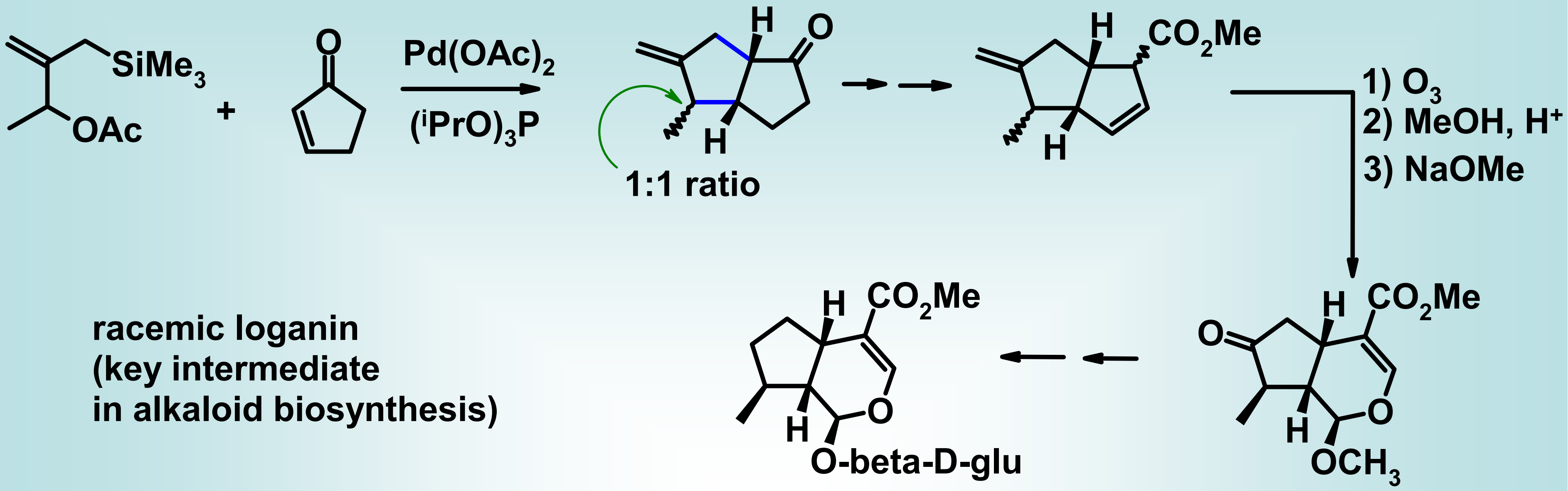
-regardless, it doesn't matter (much),

-the produc is as if......



-no *real* mechanistic explanation for this result

-example of use in synthesis - loganin



racemic loganin
(key intermediate
in alkaloid biosynthesis)

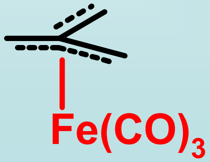
-there is *some* work on reacting TMM-Pd complexes with C=O and C=N-EWG in the presence of R_3Sn-X co-catalysts

-see Trost, B. M. et al J. Am. Chem. Soc. 1990, 112, 408.
Trost, B. M. et al J. Am. Chem. Soc. 1993, 115, 6636.

For reviews in the area see:

Trost <u>R</u> *Angew. Chem. Int. Ed. Engl.* <u>1986,</u> *25*, 1.
<u>R</u> *Pure Appl. Chem.* <u>1988</u>, *60*, 1615.
<u>R</u> 'Comprehensive Organic Synthesis' V. 5, p. 271 (1991)
<u>R</u> *Org. React.* <u>2002</u>, *61*, 1.

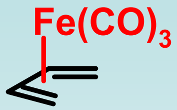
Iron tricarbonyl - trimethylenemethane complexes also known



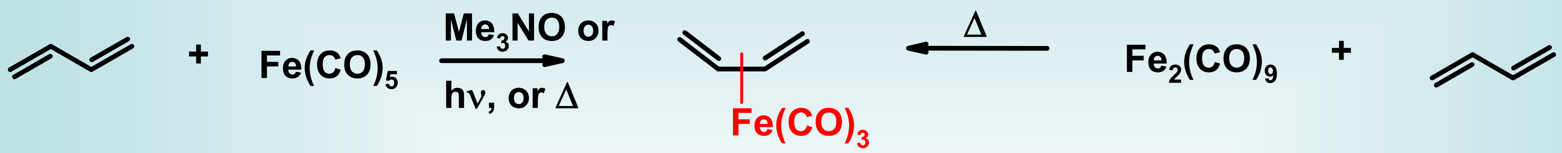
see Donaldson, W.A. *J. Org. Chem.* <u>1995</u>, *60*, 1611.
Frank-Neumann, M. *Tetrahedron: Asymm.* <u>1996</u>, *7*, 3193.
<u>R</u> Green, J. R.; Donaldson, W.A. 'Encyclopedia of Inorganic Chemistry, Vol. 4, 1994

η^4-Diene Complexes

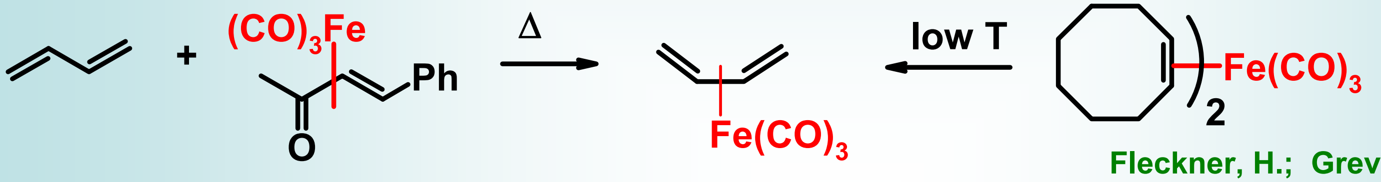
-absolutely dominated by iron tricarbonyl complexes



Preparation



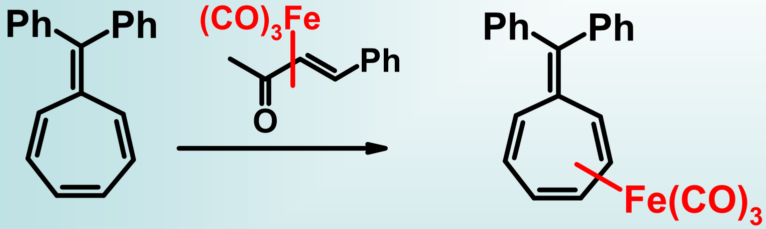
-more subtle reagents

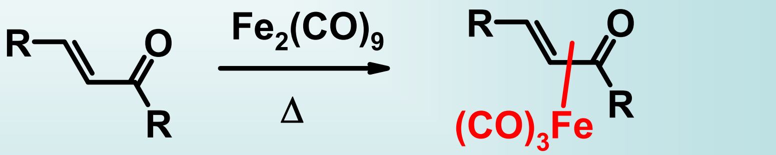


Fleckner, H.; Grevels, F.W.; Hess, D.
J. Am. Chem. Soc. 1984, *106*, 2027.

Me_3NO mediated transfer Shvo, Y.; Hazum, E. *J. Chem. Soc. Chem. Commun.* 1975, 829

-the $Fe(CO)_3$ unit is unusually stable; even in cases where it could lose more CO ligands, it normally does not



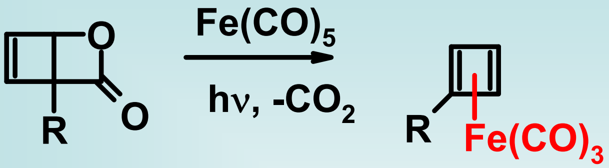


Note: esters, amides only form η^2-$Fe(CO)_4$ complexes

Reviews

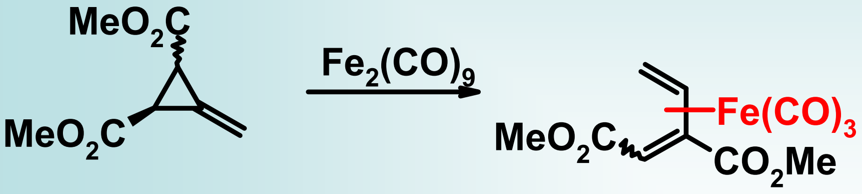
R Pearson, A.J. 'Iron Compounds in Organic Synthesis, Ch. 4, 1994.
R Green., J. R,; Donaldson, W. A. 'Encyclopedia of Inorganic Chemistry, 1994, Vol. 4
R Gree, R. Lellouche, J. P. *Adv. Met.-Org. Chem.* 1995, *4*, Ch.4
R King, R.B. 'The Organic Chemistry of Iron', Vol. 1, 1978.

Rare/specialty methods



Agar, J.; Kaplan, F.; Roberts, B. W. *J. Org. Chem.* <u>1974</u>, *39*, 3451.

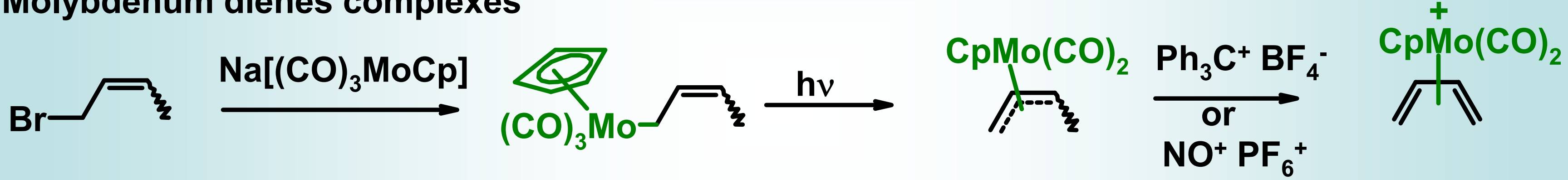
Very stable complex
-by contrast, free cyclobutadiene is <u>not at all</u> stable

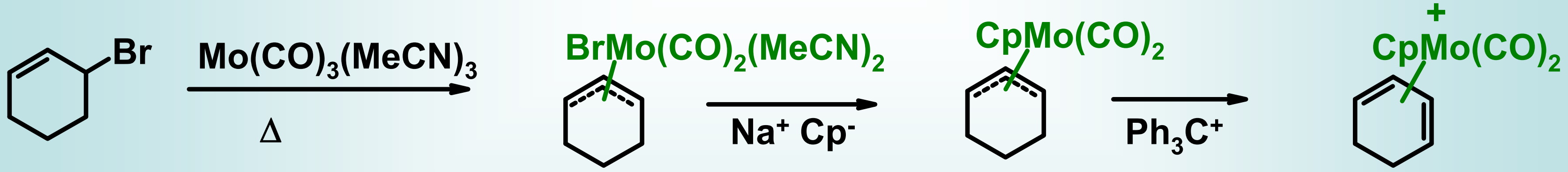


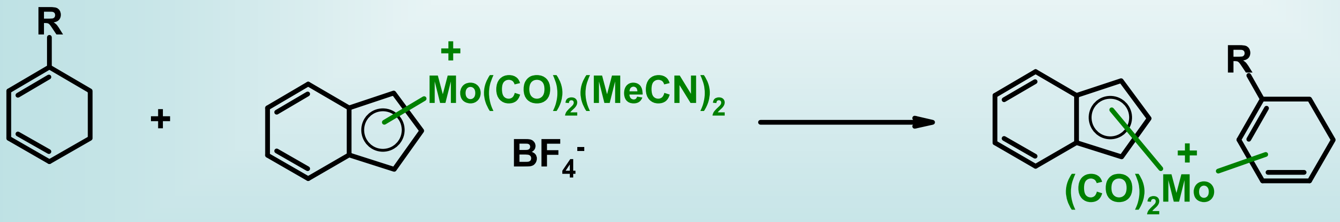
rare: ring opening is actually stereospecific

Whitesides, T.H. *J. Organomet. Chem.* <u>1974</u>, *67*, 99.

Molybdenum dienes complexes



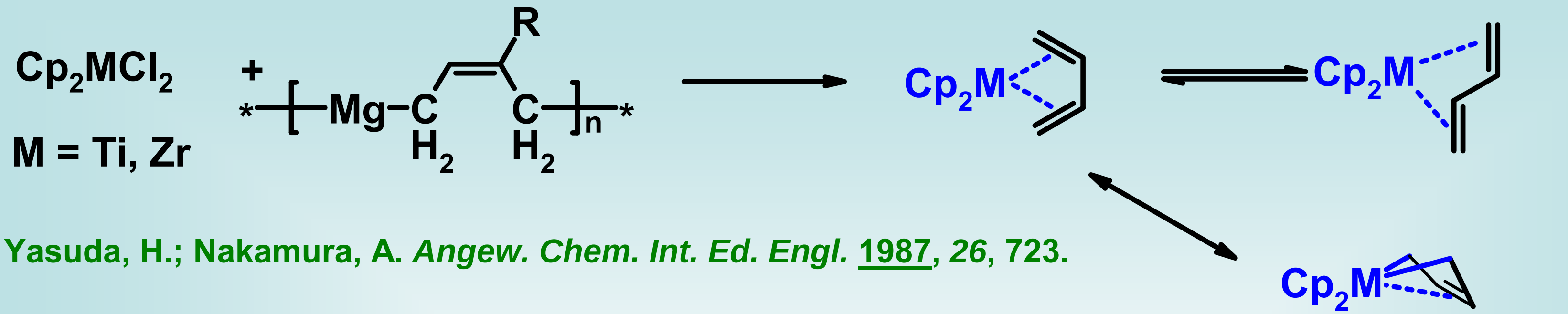




Green, M. et al
J. Chem. Soc., Chem.
Commun. <u>1985</u>, 18.

<u>R</u> Comprehensive Organometallic Chemistry, V.3, Ch 27.2
<u>R</u> Pearson, A. J. *Adv. Met-Org. Chem.* <u>1989</u>, *1*, 1.

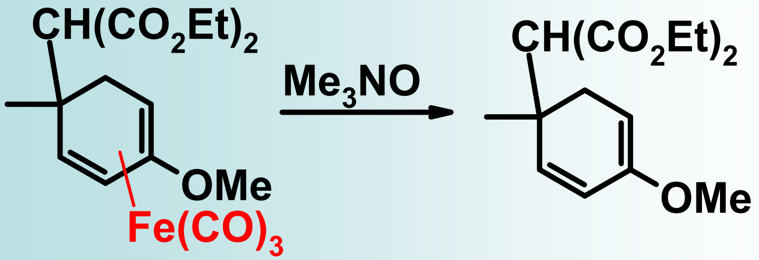
Early Transition Metal Complexes

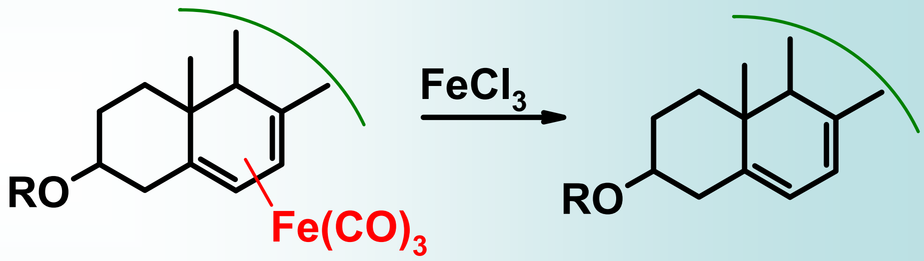


R Yasuda, H.; Nakamura, A. *Angew. Chem. Int. Ed. Engl.* 1987, *26*, 723.

2. Decomplexation of η^4-Diene Complexes

a) Oxidation of Iron-Diene Complexes





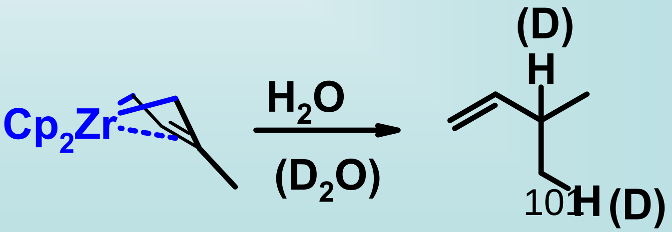
Shvo, Y.; Hazum, E. *J. Chem. Soc., Chem. Commun.* 1974, 336.

Other oxidants such as Ce^{IV}, $CuCl_2$, Ag^I work also

b) Early Transition Metal Dienes

-have reactivity like.....

and therefore



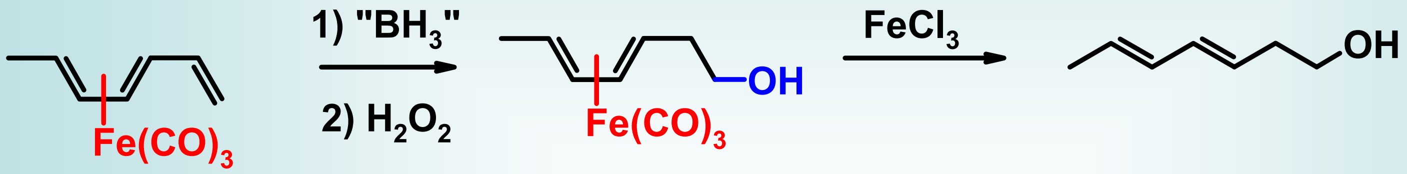
notice regiochemistry

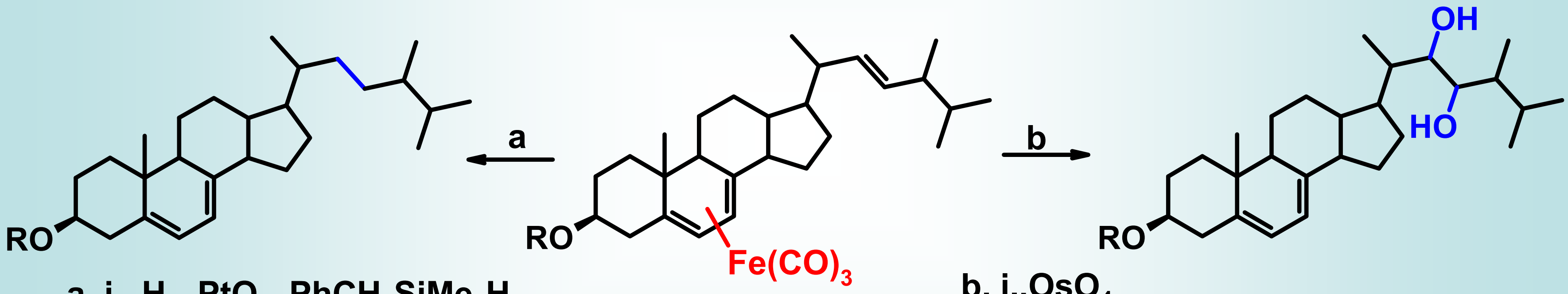
3. Use as Protecting/Stabilizing Groups

a) Protection of Dienes

-although coordination of a diene by $Fe(CO)_3$ is inductively a <u>slight</u> electron donor, the reactivity of dienes to electrophiles is *reduced*

therefore

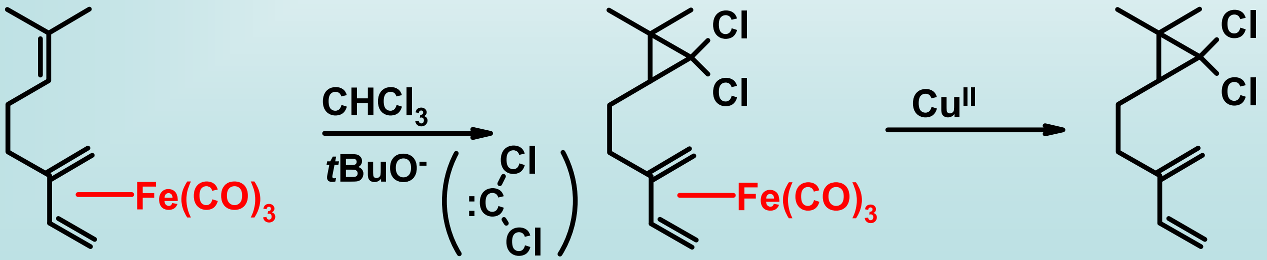




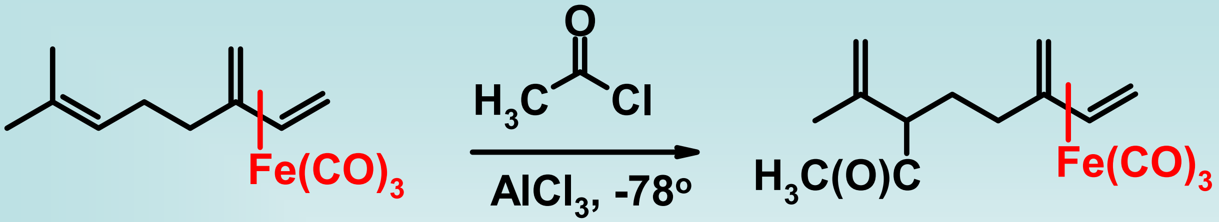
a. i., H_2, PtO_2, $PhCH_2SiMe_2H$
ii., $FeCl_3$

b. i.,OsO_4
ii., $FeCl_3$

-Carbenes - normally prefer to add to conjugated dienes over isolated C=C 's, but....

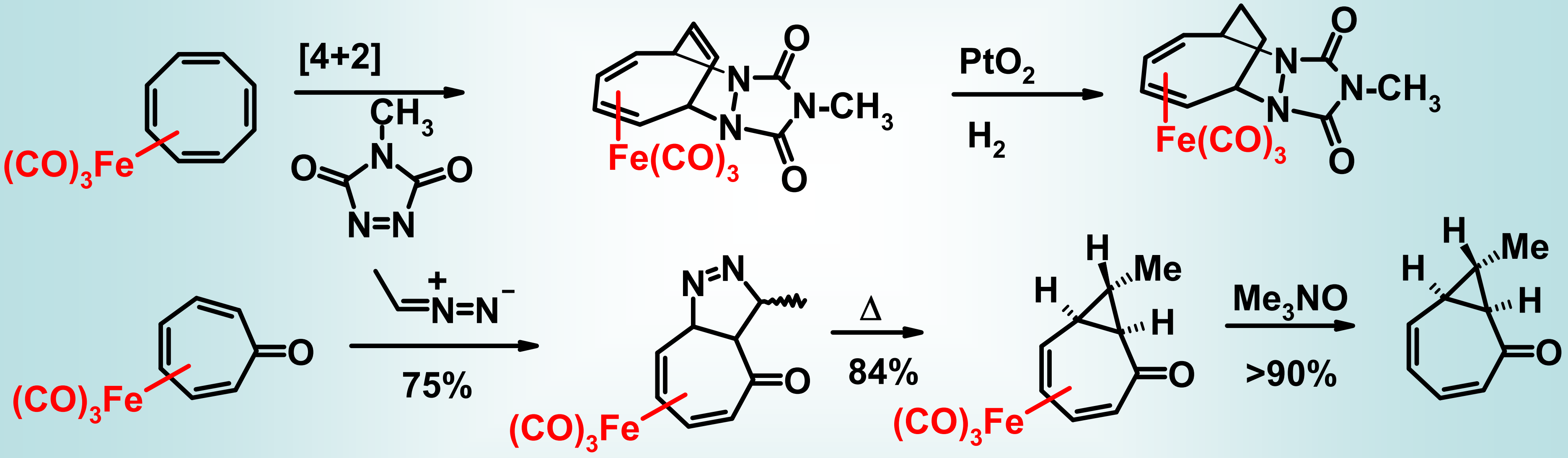


-and acylation*



* - diene-Fe(CO)$_3$ complexes *will* also react, but more slowly

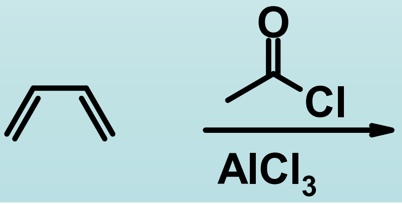
-one can even do cycloadditions on free double bonds in the presence of Fe(CO)$_3$ complexes



-also stable to Wittig reaction, aldol condensations, osmylation (dihydroxylation)

-exception (sort of) - let's say 'controlled' reactivity

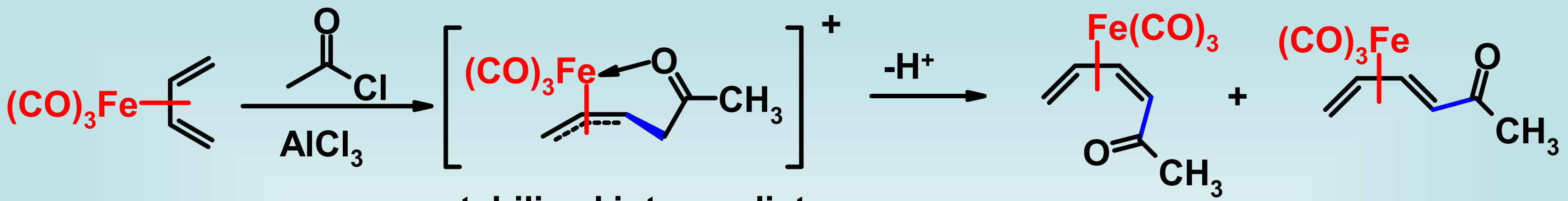
consider



a mess

v. non-selective reaction/oligomerization

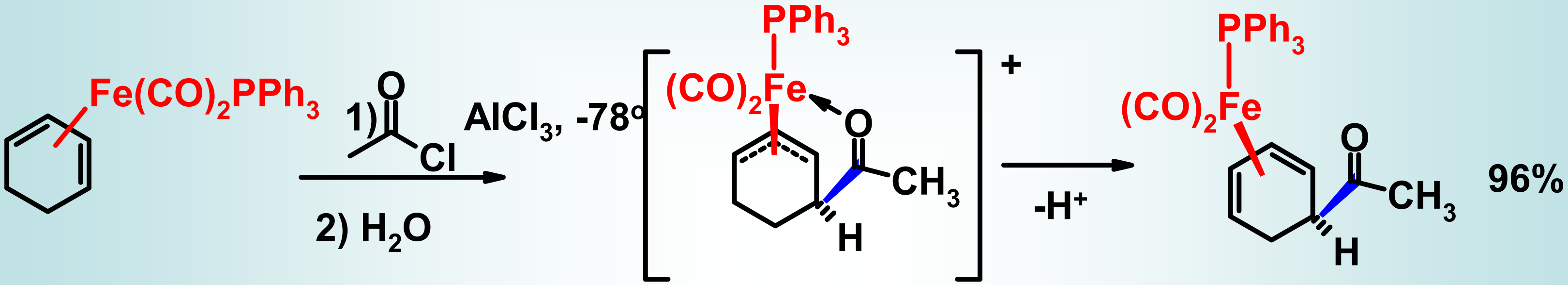
-conversely,..



stabilized intermediate

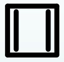
depending upon conditions

-the reactivity is lower, but much more controlled



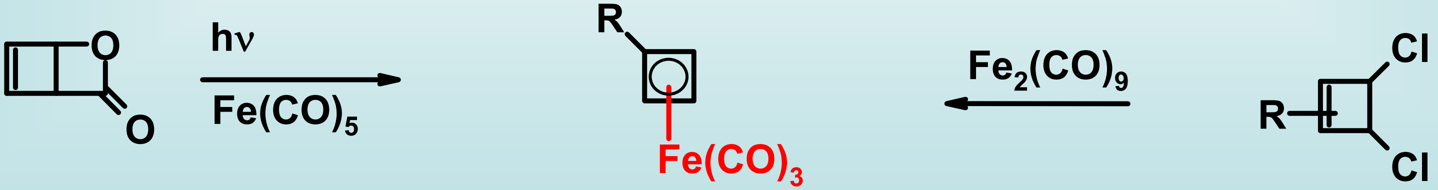
b) Stabilization of (overly) Reactive Species

i) consider cyclobutane



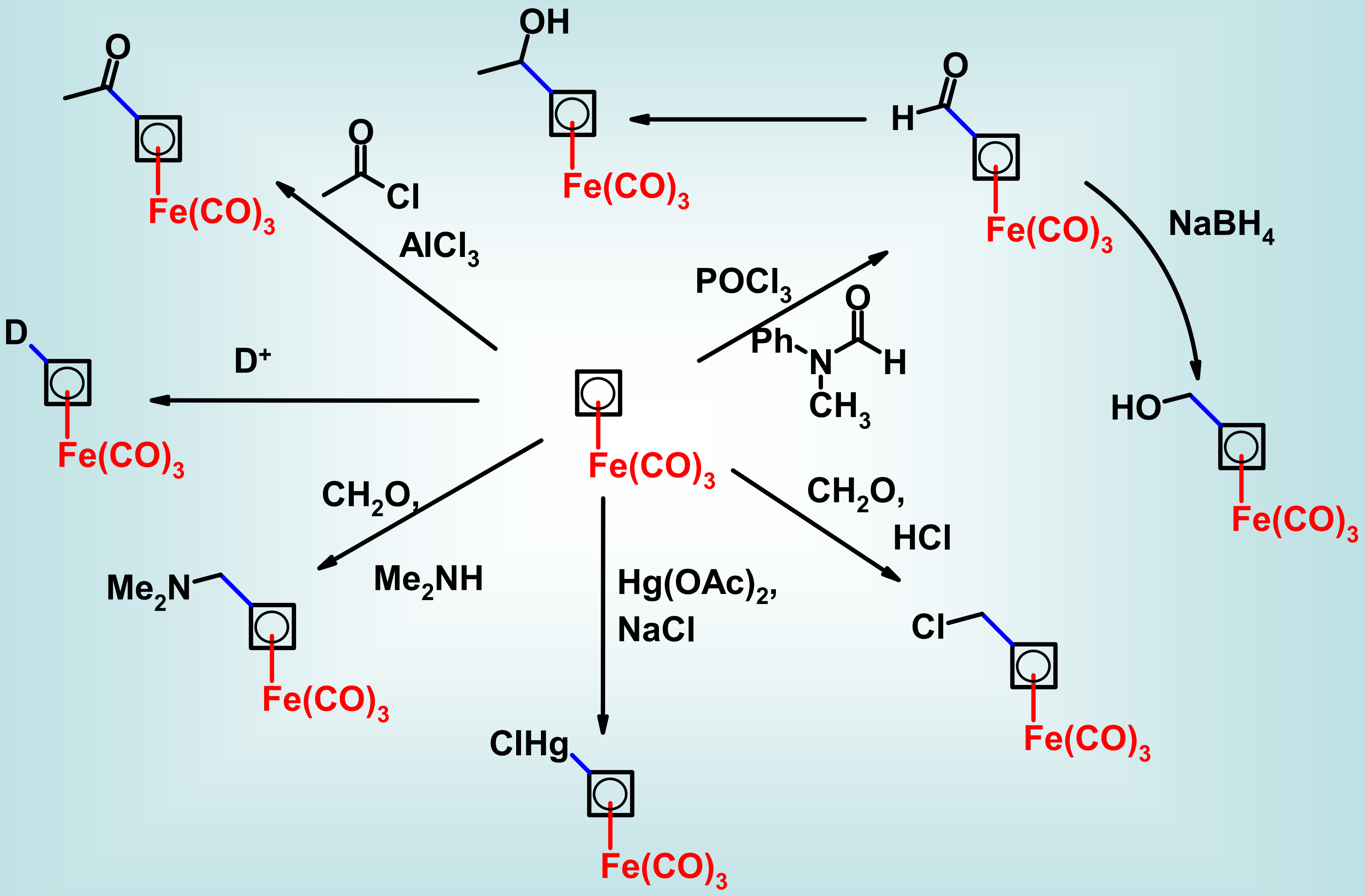
-classic antiaromatic compound
-'cannot' be isolated

-very stable compounds



-stable enough to allow standard aromatic functionalization reactions - behaves pretty much like benzene

-these cyclobutadiene-Fe(CO)$_3$ complexes are stable enough to allow standard aromatic functionalization reaction - they behave pretty much like benzene

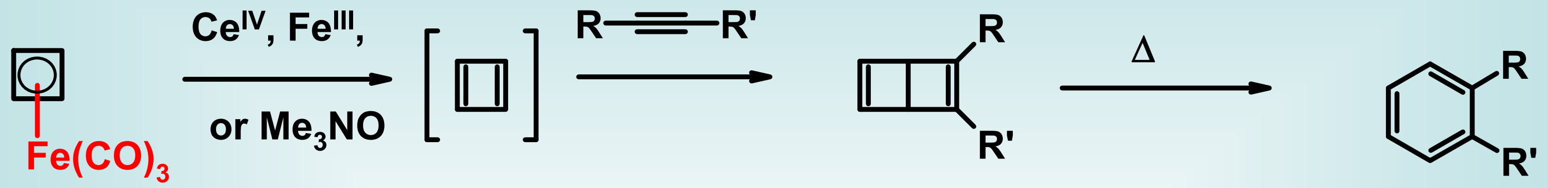


Rosenblim, M.; et al *J. Am. Chem. Soc.* 1972, *94*, 1239

Emerson, G.F.; Pettit, R., et al *J. Am. Chem. Soc.* 1975, 97, 3255.

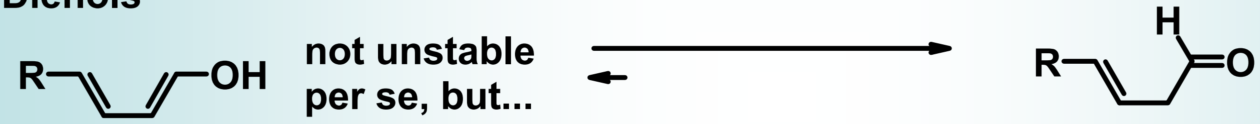
R Green, J. R.; Donaldson, W.A. 'Encyclopedia of Inorganic Chemistry', Vol. 4, 1735, 1994.

Note: Decomplexation of Fe leads to free cyclobutadiene, which can be trapped by other reagents



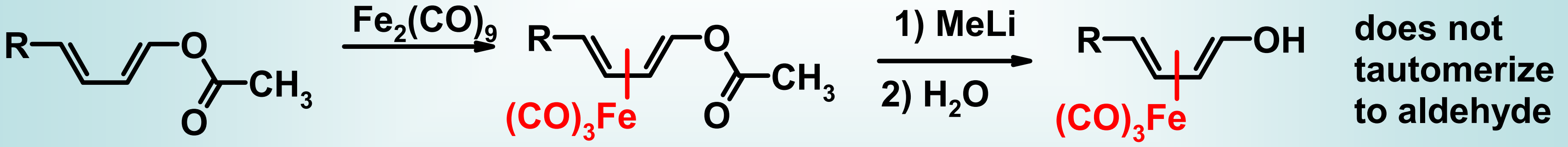
Pettit, R. *J. Am. Chem. Soc.* 1965, *87*, 3253.
Snapper, M.

ii) Dienols

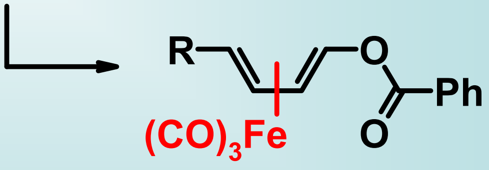


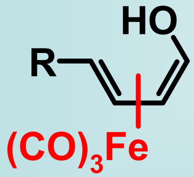
not unstable per se, but...

Fe(CO)$_3$ coordinates more strongly to the π-system of a C=C relative to a C=O, so....

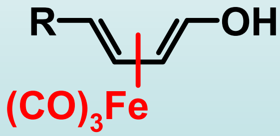


does not tautomerize to aldehyde

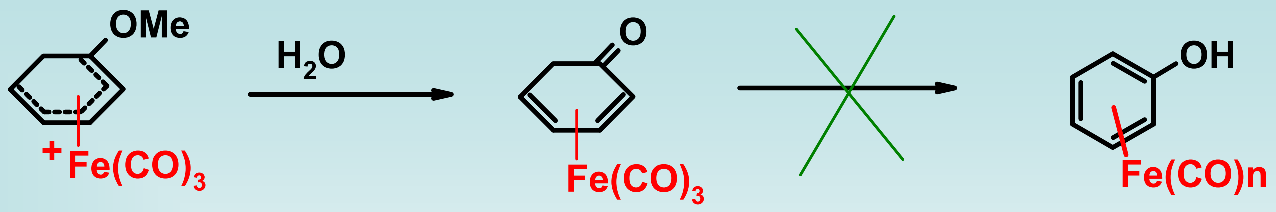




is similar, except it isomerizes to....



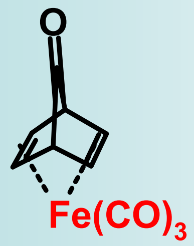
iii)



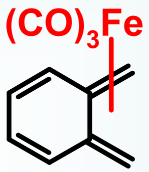
-almost nothing has been done with this, but it has much potential....

see Birch, A.J. *Tetrahedron Lett.* 1975, 119 (*Org. Synth.* VI, 996)

iv) Other examples



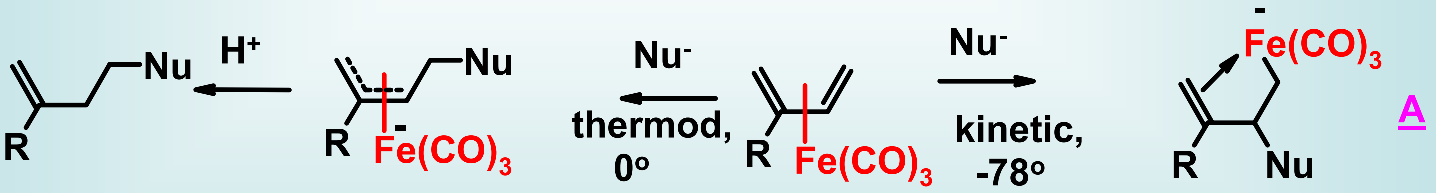
Landesberg, J.M.;
Sieczkowski, J.
J. Am. Chem. Soc. 1971, *93*, 972

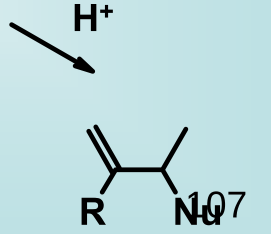


Roth, W.R.; Neier, J.D.
Tetrahedron Lett. 1967, 2053.

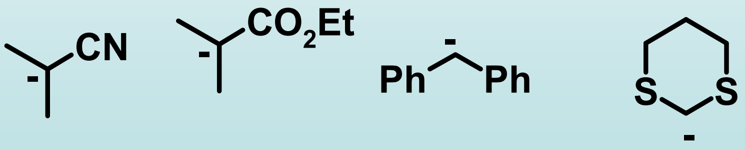
4. η^4 Diene Iron Complexes as Electrophiles

-iron diene complexes will react with nucleophiles, although the pathways are a bit complex



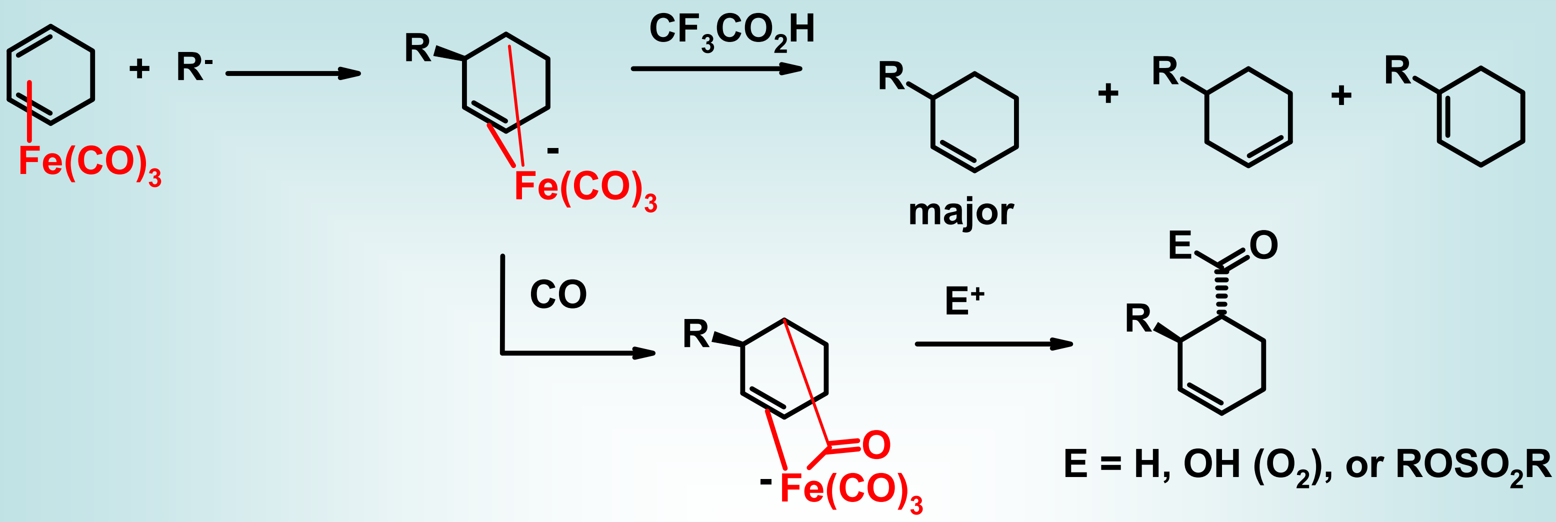


Nucleophiles are restricted to things like..........



Semmelhack, M.F. *J. Am. Chem. Soc.* 1984, *106*, 2715.

-in cyclohexadiene complexes, species like A do further chemistry



E = H, OH (O_2), or $ROSO_2R$

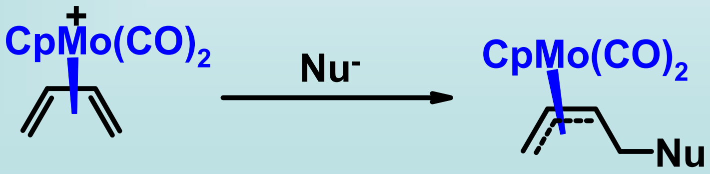
-see R Pearson, A.J. 'Iron Compounds in Organic Synthesis, p. 67-97.

in acyclic dienes, get related but more complicated reaction pathway

-see Semmelhack, M. F. *Organometallics* 1983, *2* 1385 ; *J. Am. Chem. Soc.* 1985, *107*, 1455.
Yeh, M.C.P.; Hwu, C.C. *J. Organometal. Chem.* 1991, *419*, 341.
Chang, S. et al (M. Brookhart) *J. Am. Chem. Soc.* 1994, *116*, 1869.

b) Molybdenum Diene Complexes

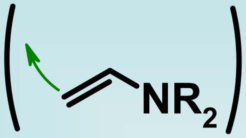
-these complexes are cationic, so that they obviously are a good choice for being more reactive as electrophiles



C-1 attack

-range of nucleophiles should start looking familiar

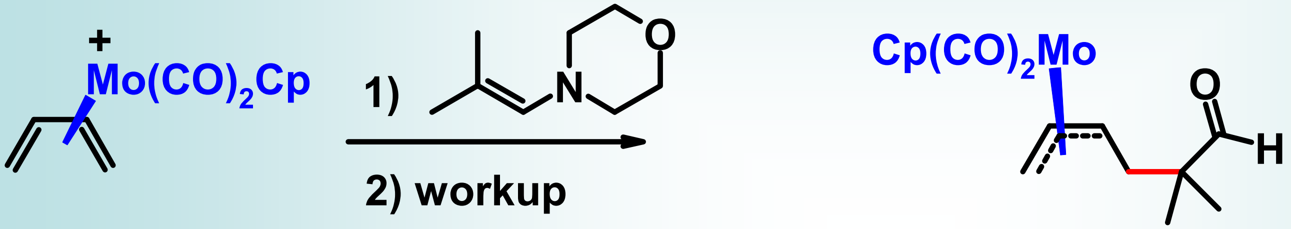
-enamines

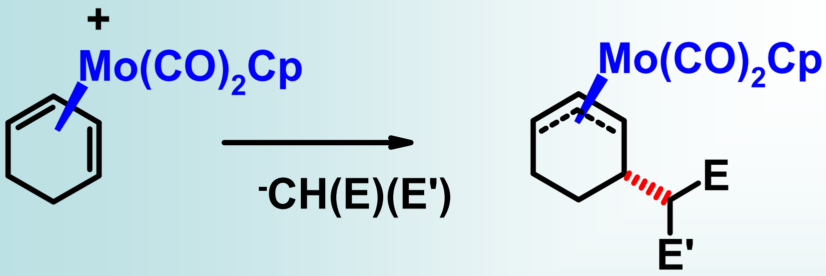


highly stabilized enolates ($^{-}CH(CO_2Et)_2$)

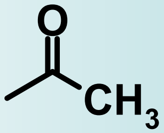
Grignards, or better still, cuprates

($RMgBr$, R_2CuLi, $R(CN)CuZnI$)

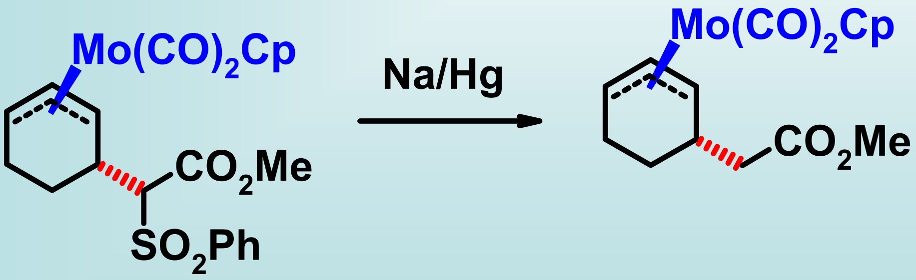


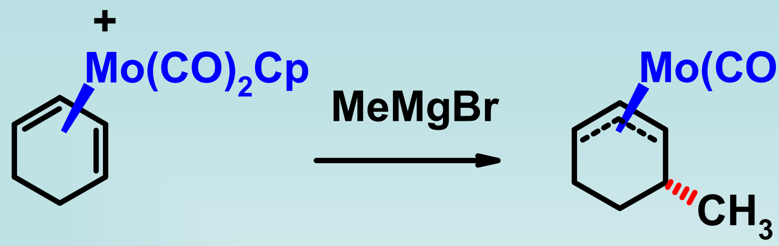


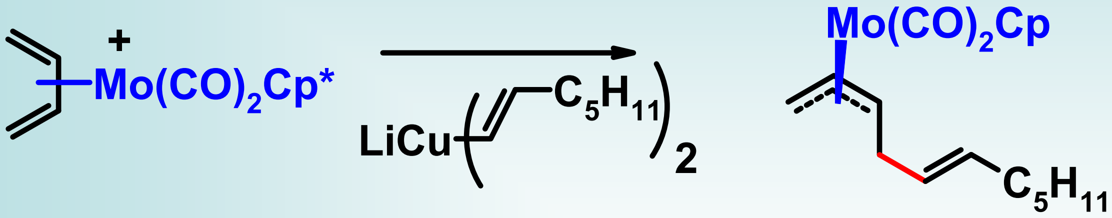
E, E' = $-CO_2Me$, $-SO_2Ph$,



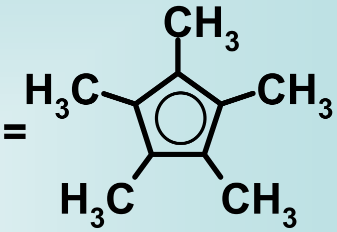
Note:







Note: Cp* =



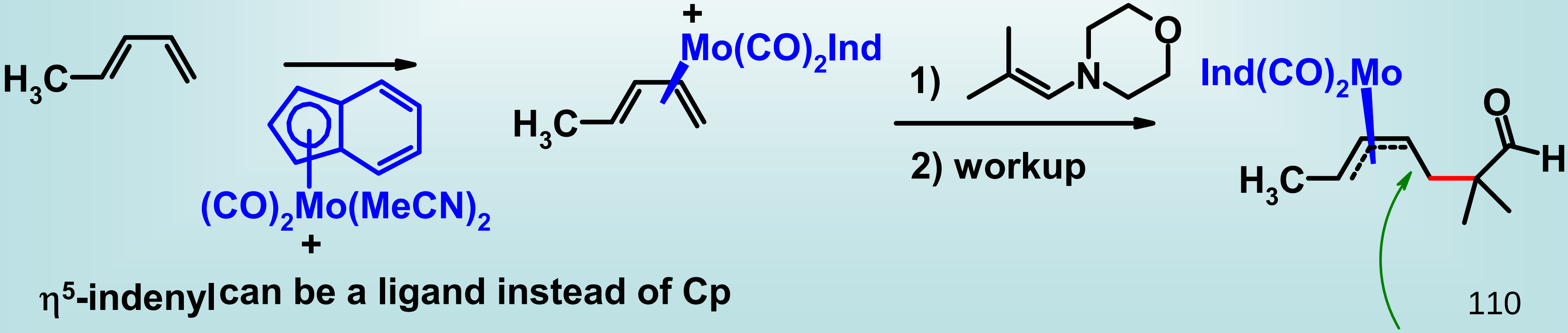
can be a ligand on Mo instead of Cp

Stereochemistry

-it is apparent from the above examples that the addition is routinely *anti* to Mo

Regiochemistry

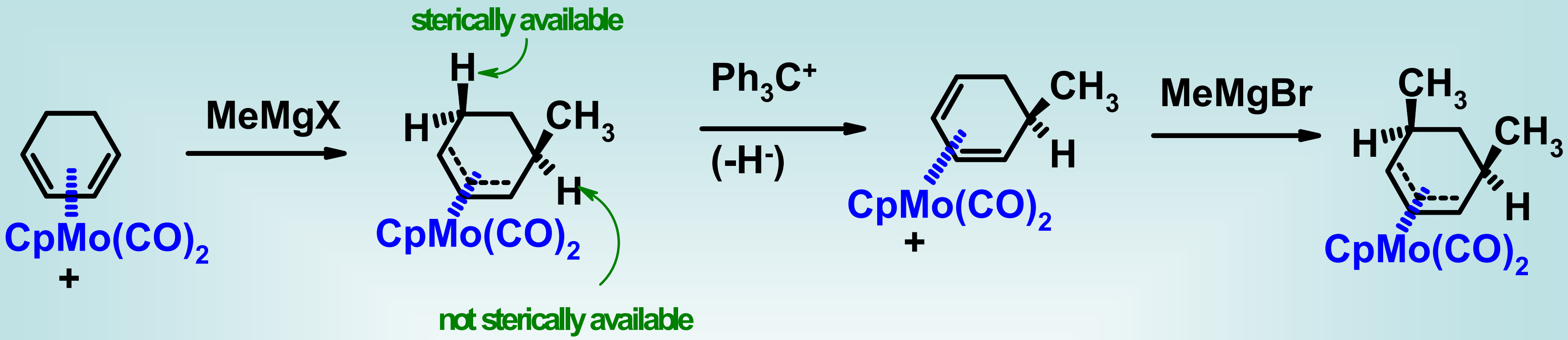
-the nucleophile's attack is generally at the less substituted end of the diene



η^5-indenyl can be a ligand instead of Cp

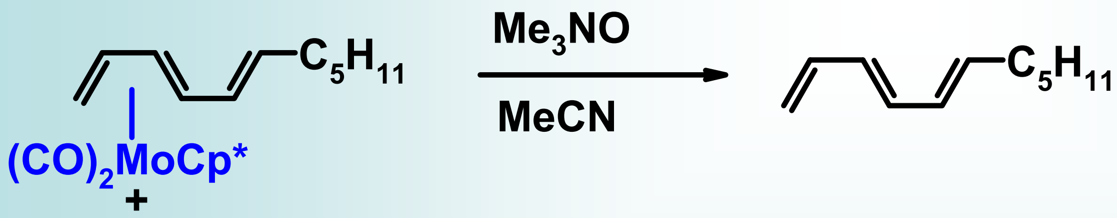
Note; product allylMo has *anti* stereochemistry at addition site

-tandem reactions are also feasible

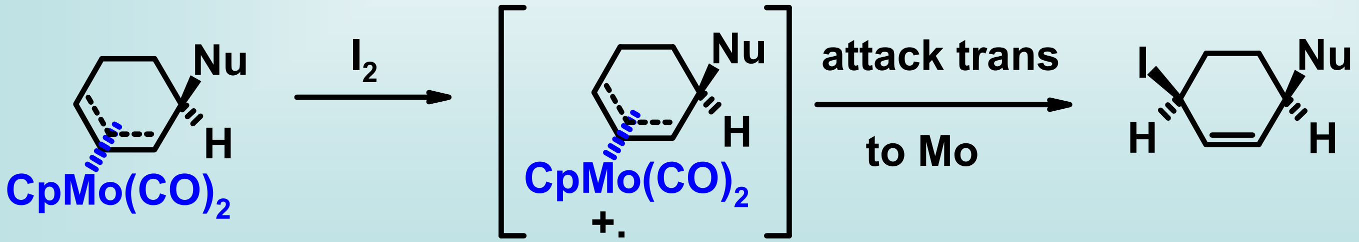


Decomplexation Reactions of molybdenum Complexes

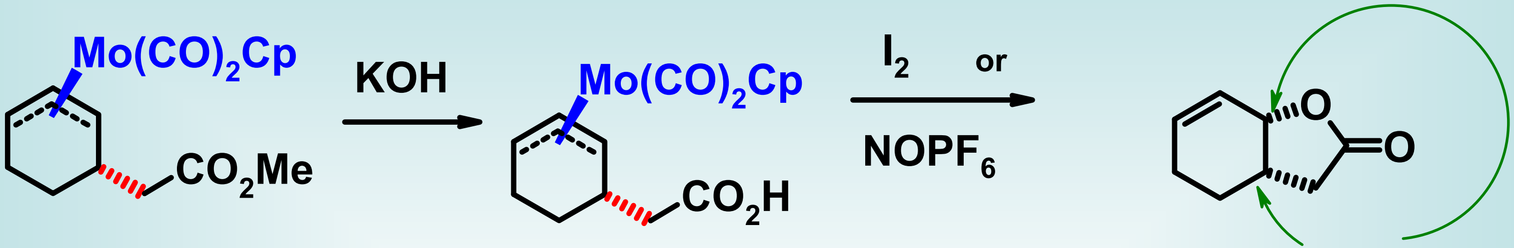
-straight oxidative decomplexation does occur for diene complexes



-oxidative decomplexation of allylMo's with nucleophilic attack



-oxidative decomplexation can occur with nucleophilic addition

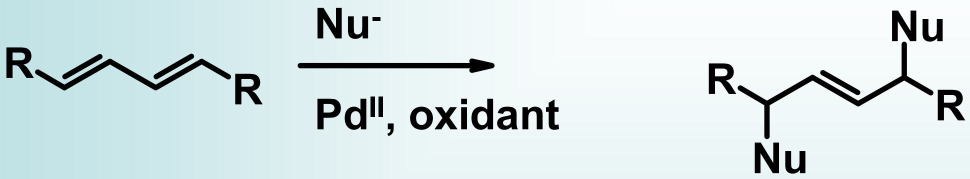


-note stereochemistry

R Pearson, A.J. *Adv. Met. Org. Chem.* 1989, *1*, 1.
R Backvall, J.-E. *Adv. Met. Org. Chem.* 1989, *1*, 135. (mostly Pd catalyzed addns)

asymmetric addns Pearson, A.J. et al *Tetrahedron Lett.* 1987, *28*, 2459

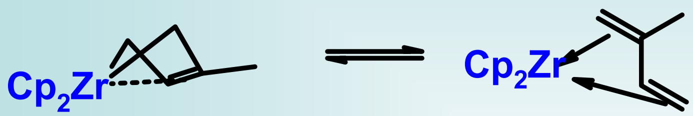
c) we will not discuss this in detail, but Pd^{II} catalyzed additions to dienes is known



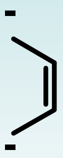
Nucleophile is usually R_2N^- or AcO^-; oxidant is usually benzoquinone
some cases of C-C bond formation
-see Backvall review

η^4-Diene Complexes as Nucleophiles

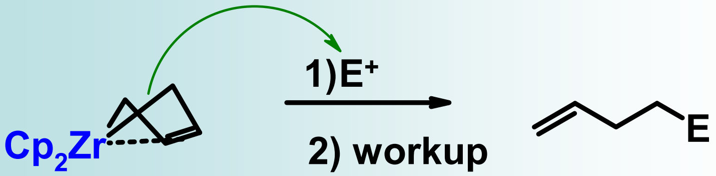
-early transition metal diene complexes don't really behave like dienes
-dominated by Cp_2Zr complexes



behaves like

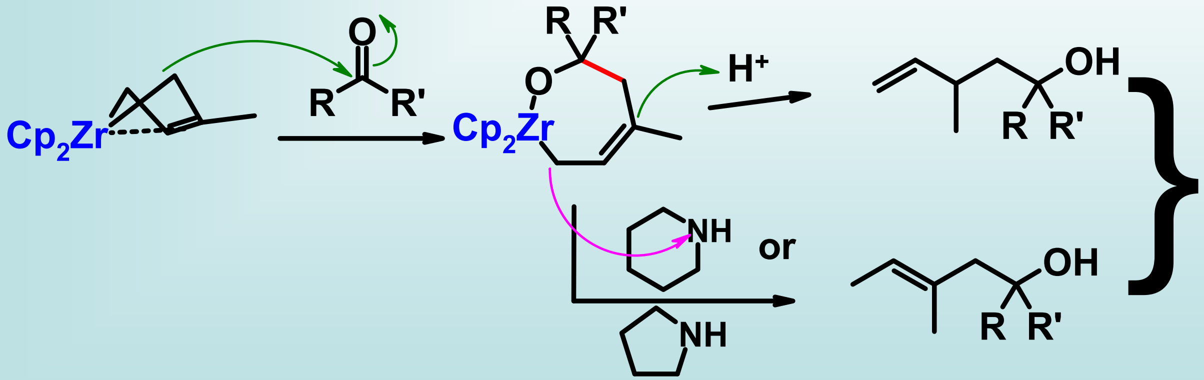


-therefore, the zirconium dienes are reactive as nucleophiles, especially with oxygen containing electrophiles, where =O: coordination to Zr can increase the electrophilicity of C=O



Regiochemistry

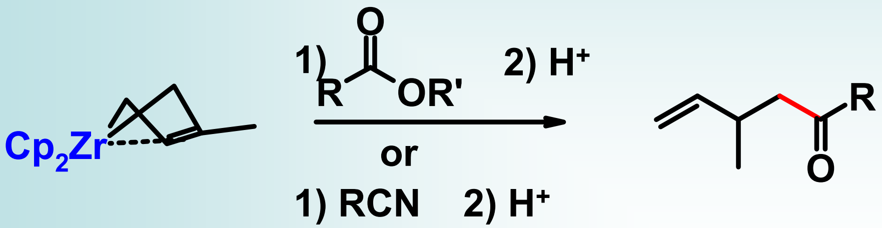
-if a substituent is at the 2-position of the diene, the rxn occurs at the <u>more</u> substituted end

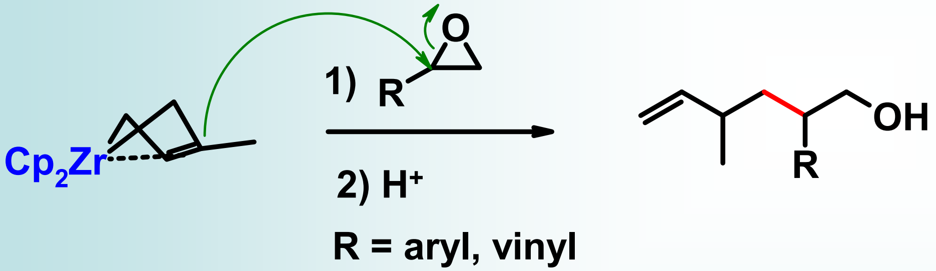


notice difference in product isomer dependence on acid vs. base cleavage

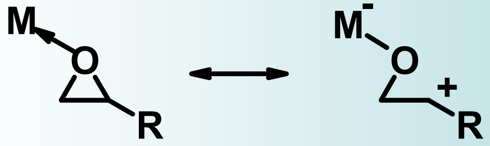
-in acid, the allylZr cleaves via S_E2' (remote end, much like allylsilanes)
-in base, the product is the result of direct C-Zr bond cleavage

-other oxygen bearing E^+'s include......
esters (or nitriles), and epoxides

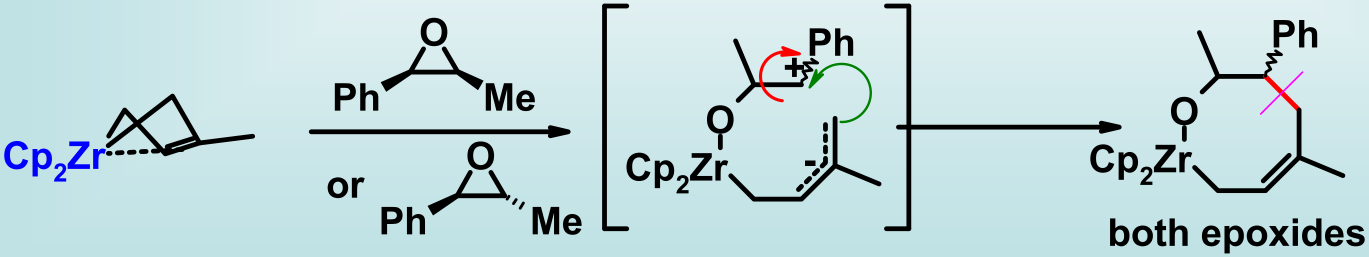




Note: Rxn is at the more substituted end of the epoxide



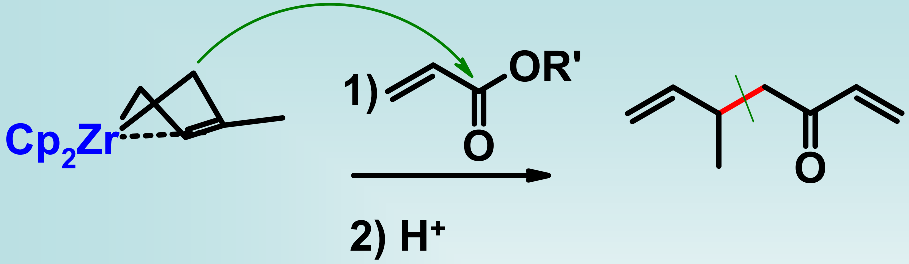
-that is evidence of S_N1 - type reactivity
-further evidence is the loss of stereochemical integrity of the epoxide, i.e.,

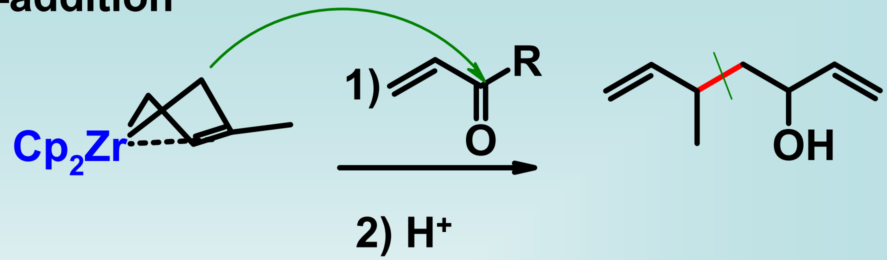


both epoxides give
same isomeric mixture

α, β-unstaurated carbonyls

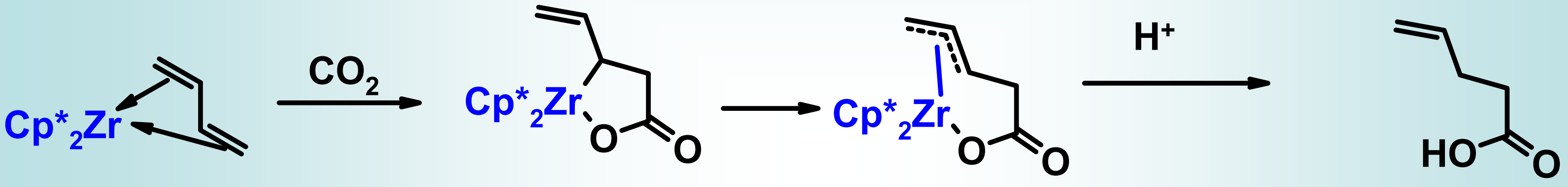
-give high 1,2-addition





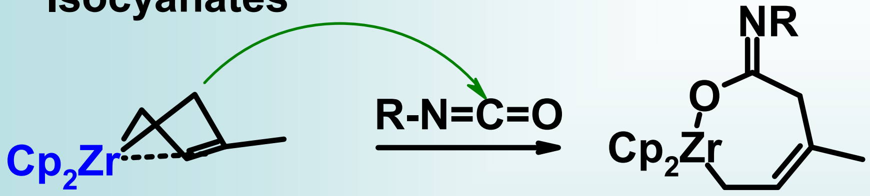
Other electrophiles

CO_2



But in many cases, further reaction can't be stopped

Isocyanates

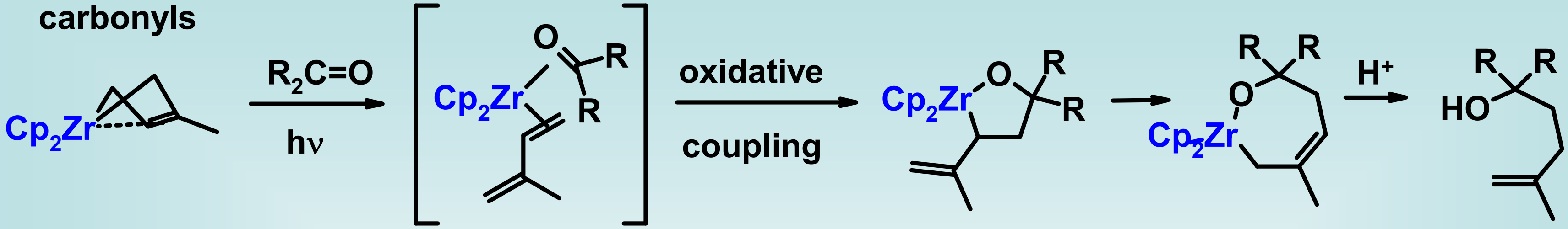


Photochemical Reactions

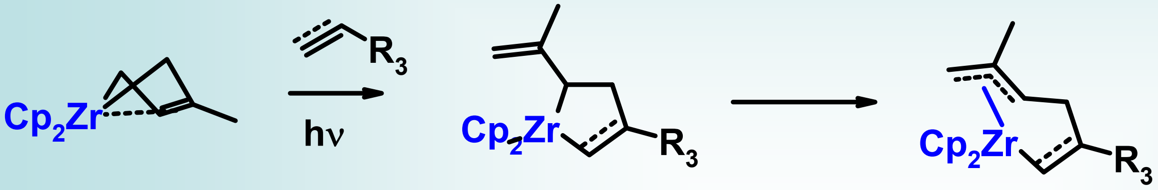
-with carbonyl compounds and alkenes/alkynes, a photochemical reaction occurs at much lower T (-70°)

-one big difference - the reaction now occurs <u>away</u> from a 2-substitutent

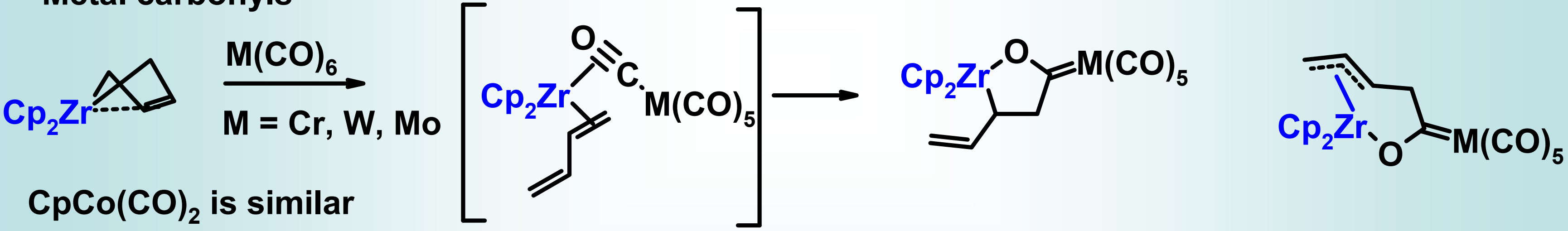
carbonyls



alkenes/alkynes

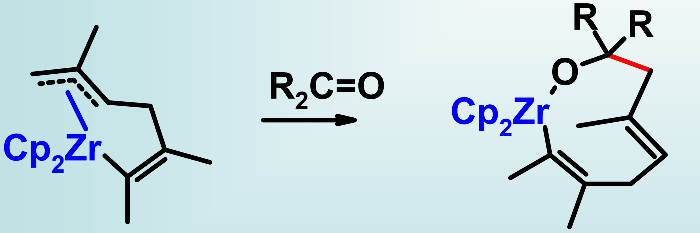


Metal carbonyls



CpCo(CO)$_2$ is similar

Finally, at least for some products, the allylZr products themselves can be reacted with carbonyls



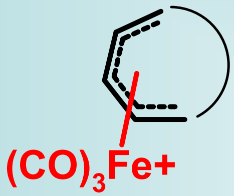
carbonyl, metal carbonyl adducts do this to
-always get 9-membered ring with trans C=C

see R Yasuda, H.; Nakamura, H. *Angew. Chem. Int. Ed. Engl.* 1987, *26*, 723.
R Taber, D. F. et al *Curr. Org. Chem.* 2000, *4*, 809.

other Fe diene review R Gree, R. *Synthesis* 1989, 342.

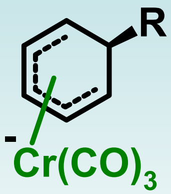
η^5-Dienyl Complexes

-dominated by



complexes

and to a much lesser extent by

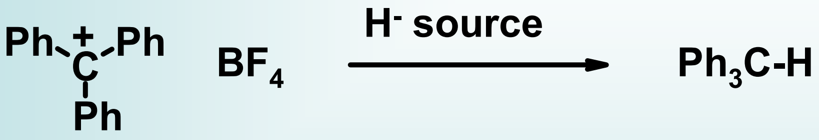


we will cover this under η^6- complexes

authors -dominated by A.J. Birch initially
-more recently by A.J. Pearson (Case Western)
W.A. Donaldson (Marquette) (acyclics)

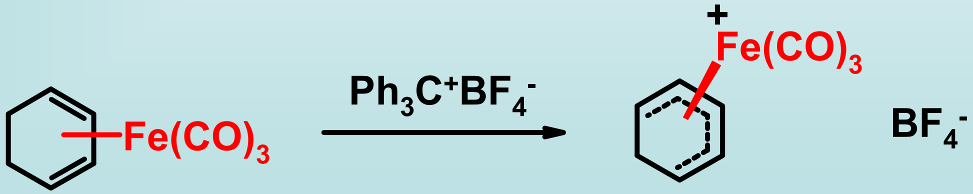
Generation of η^5-Cationic Complexes

-most commonly made by hydride abstraction from diene complexes, normally by trityl cation



triphenylmethyl (trityl) cation

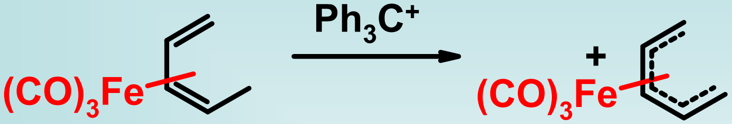
-thus....



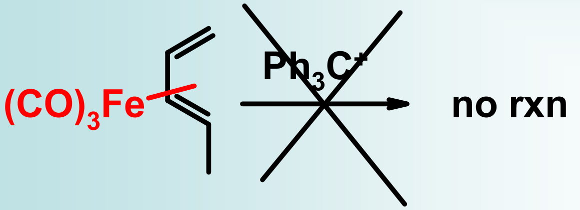
-works very well for cyclic dienes, as adjacent substituent must be ***cis***

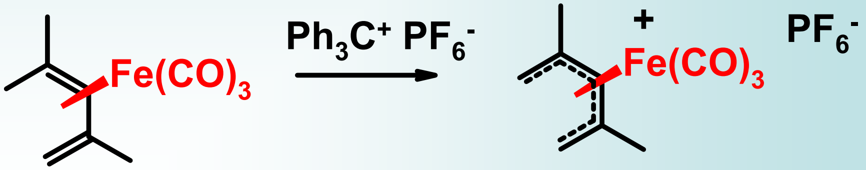
-with acyclc dienes, one can normally abstract H^- is the source is cis

i.e.,



-but, if the "H^- source' can only be trans, the abstraction usually fails





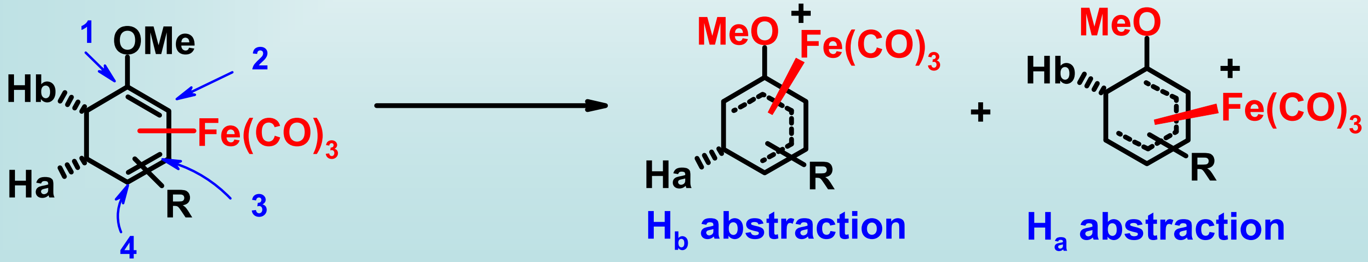
Regiochemistry of Hydride Abstraction

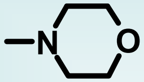
-this abstraction s usually pretty selective, but not that readily predictable. It does not correspond to the most stable cation

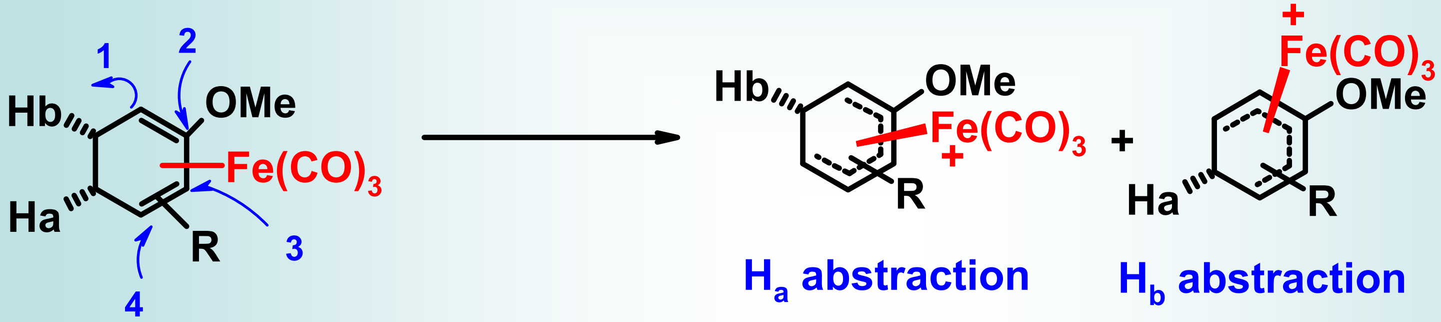
-Pearson has made an orbital interaction based explanation - for those interested, see.

Pearson, A.J. et al *Organometallics* 1984, *3*, 1150.

-examples

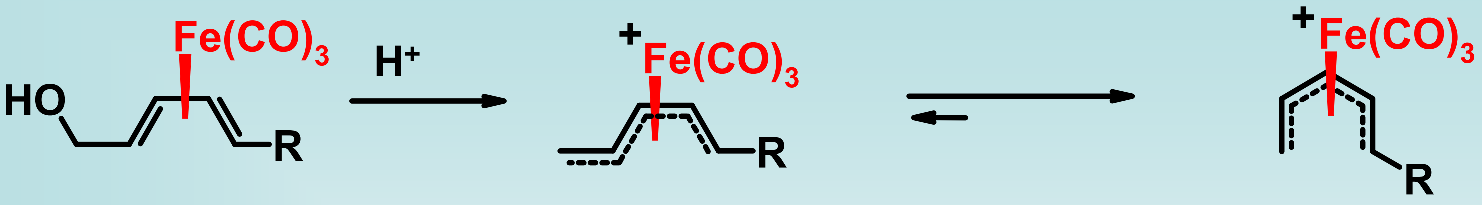


R	H_b abstraction	H_a abstraction
H	20	80
3-CH_3	0	100
4-CH_3	90	10
3-OCH_3	56	44
4-morpholino 	100	0



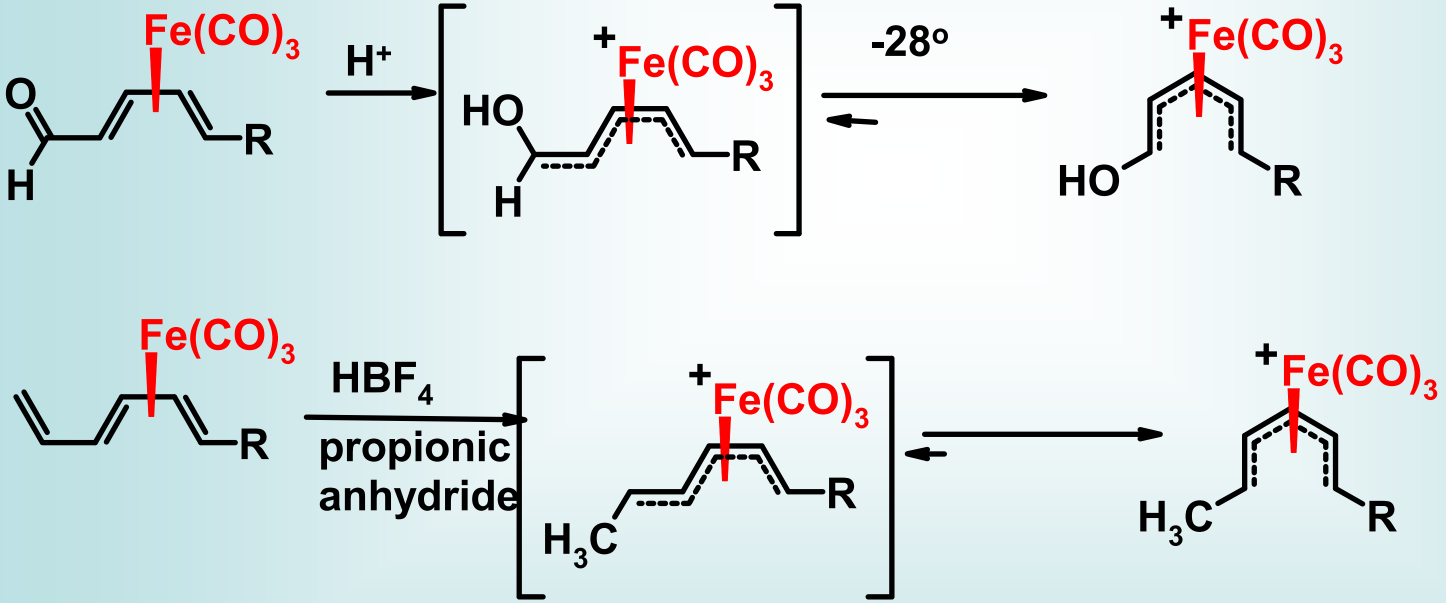
R ro	H_a abstraction	H_b abstraction
H	90	10
1-CO_2Me	100	0
4-CO_2Me	0	100
4-CH_3	0	100
4-OCH_3	56	44

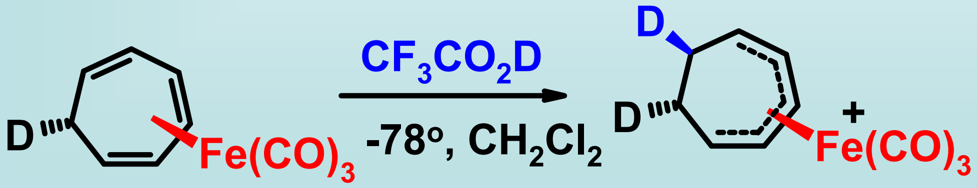
-the most common method for formation of acyclic pentadienyliron complexes is by protonation of an η^4–dienyl alcohol complex by a strong acid



see R Donaldson, W.A. *Aldrichim. Acta* 1997, *30*, 17.
also Magyar, E.S. et al *Inorg. Chem.* 1978, *17*, 1775.
Beihl, E.R. et al *J. Organomet. Chem.* 1979, *174*, 297.

-there are related methods for preparation of dienylirons, from carbonyls, alkenes (trienes)

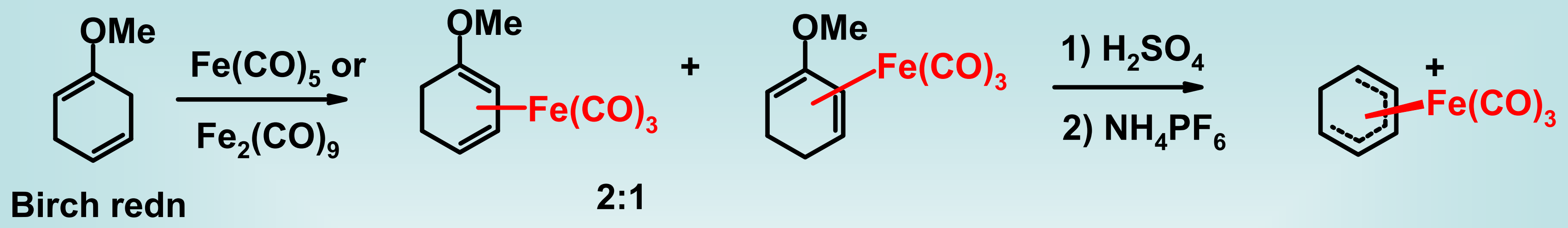




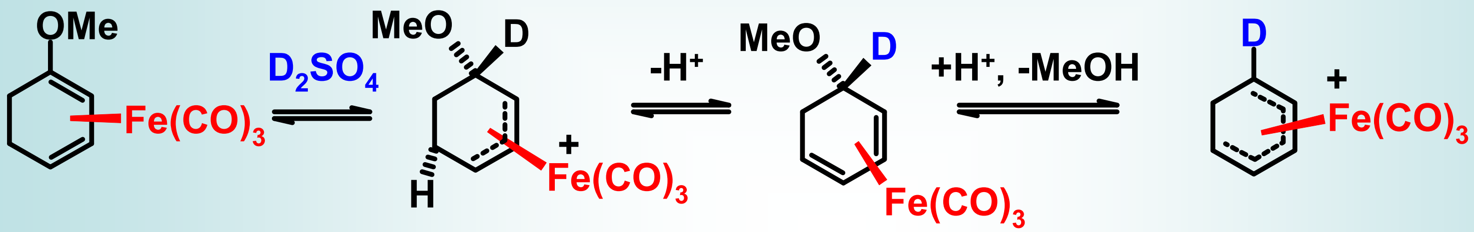
notice the stereochemistry of attack

J. Chem. Soc., Dalton Trans. 1977, 794 and 2340

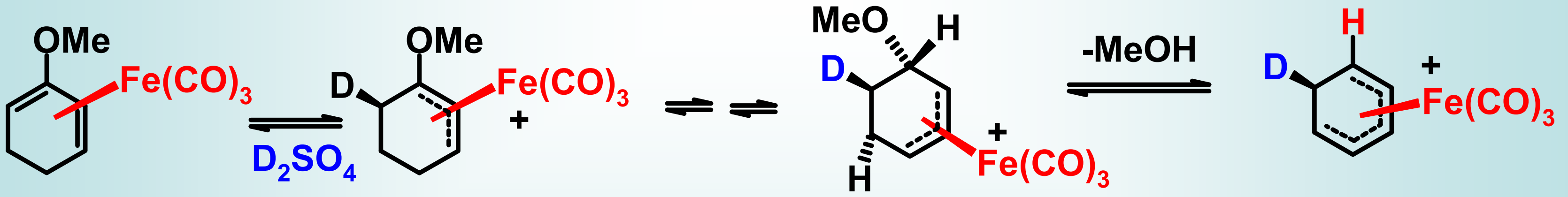
-from alkoxy-substituted diene complexes and strong acid



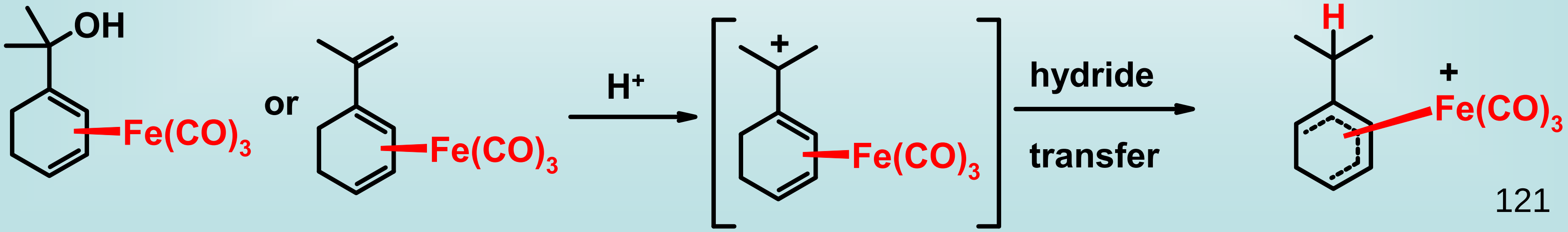
This goes via....



-and



-by cation rearrangement



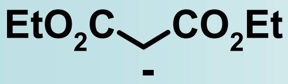
Reactions as Electrophiles

Nucleophilic Attack on η^5-Complexes

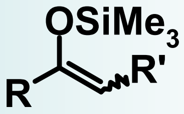
-these cations readily react (normally) with nucleophiles to give C-C or C-heteroatom bond formation

-attack is from the <u>exo</u>- face (stereoselective, away from iron)
-'normal' mode of attack is at C-1 terminus

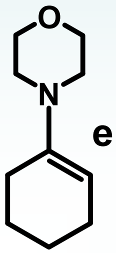
Nucleophiles: C-C bonds



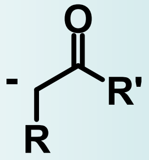
stabilized enolates



silyl enol ethers
silyl ketene acetals



enamines



enolates work
only
sometimes

allylsilanes
allyltins

RLi, RMgBr usually fail
R_2Cd, R_2Zn, R_2CuLi, RCu(CN)ZnI usually better

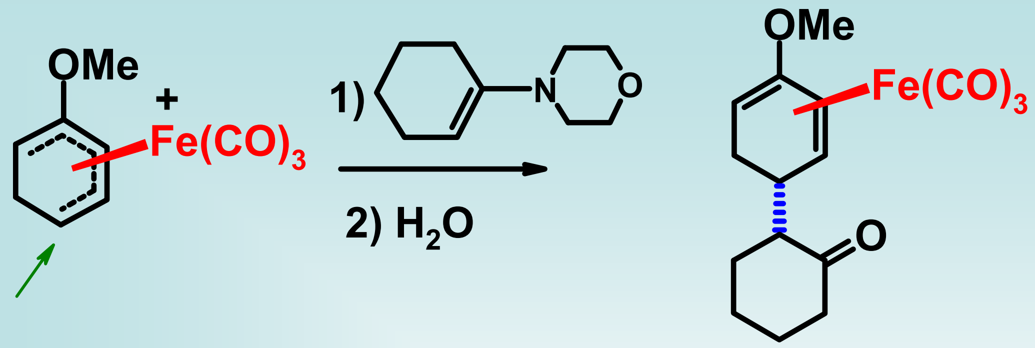
C-X bonds

R_2NH (amines), H_2O, MeO^-, R_3P (phosphines), $(RO)_3P$ (phosphites), R_3As (arsines)

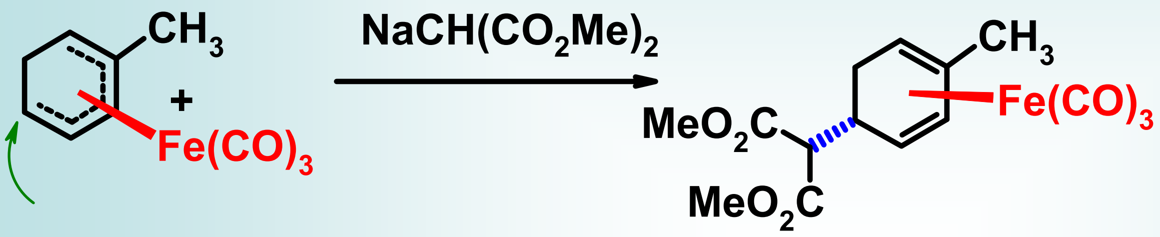
$NaBH_4$, Et_3SiH, $NaBH_3CN$ (hydride sources)

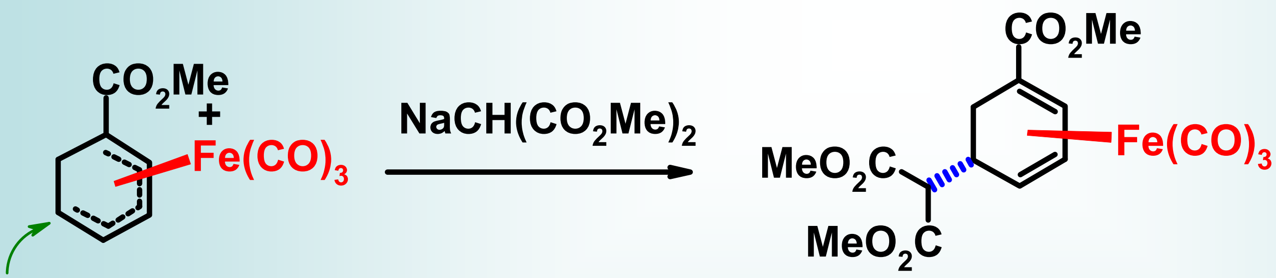
Regiochemistry, part II

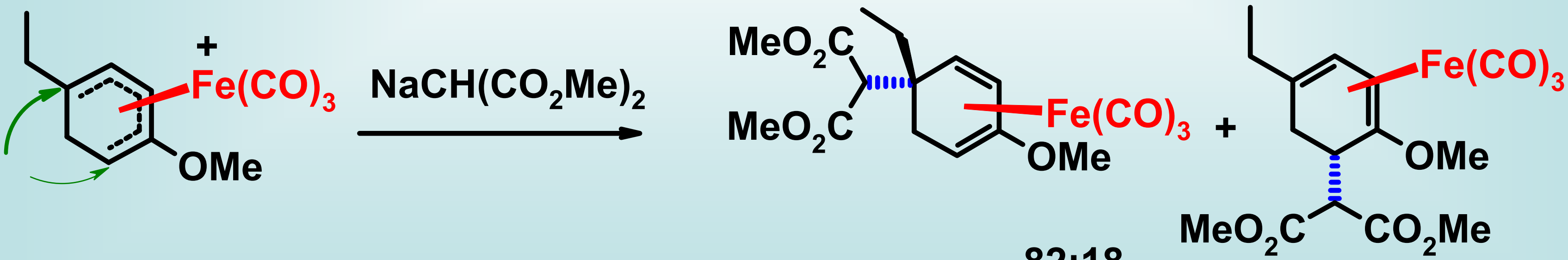
-attack of the nucleophiles is at less substituted terminus
-MeO as a substitutent is particularly powerful in this respect



- enamine example
- regiochem away from OMe
- sterochem exo (away from iron)

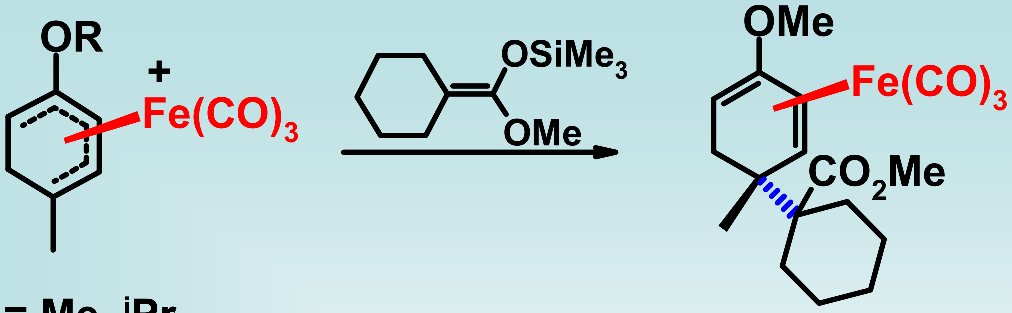






82:18

counterion dependent

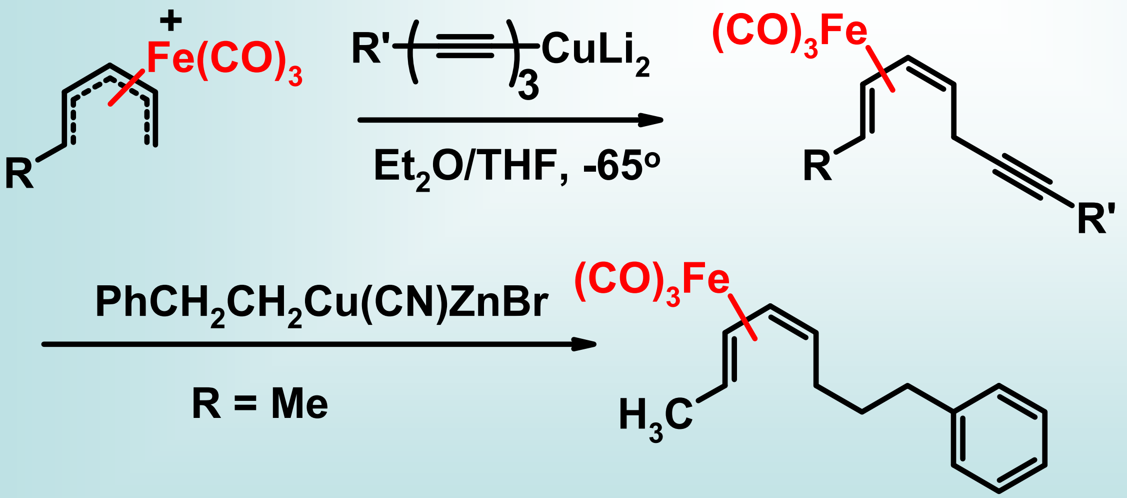


R = Me, ^{i}Pr

see **R** Pearson, A.J., in Comprehensive Organometallic Chemistry, Vol. 8, p 939-1011
R Comprehensive Organic Synthesis, 1991, Vol. 4, p. 663-694
R Iron Compounds in Organic Synthesis, 1994, Ch.5
R *Adv. Met-Org. Chem.* 1989, *1*, 1

R Harrington, P.J. Transition Metals in Total Synthesis, Ch. 4

The acyclic cases have also been studied fairly extensively

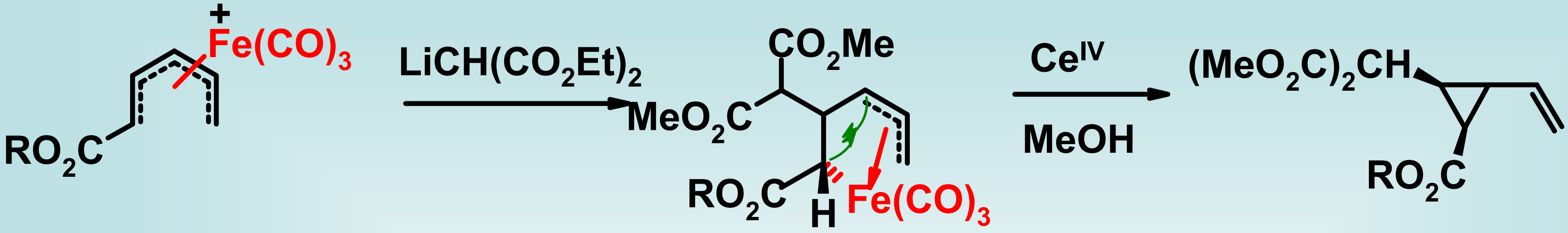


R = Me, Ph, CO_2Me

Donaldson, W. A. et al
Tetrahedron Lett. 1989, *30*, 1339.

Also, RNH_2, H_2O, R_2Cd, R'-CC-$SiMe_3$ + F^-, $NaBH_3CN$,
silyl enol ethers, allylsilanes (give trans products), and $NaCH(CO_2Et)_2$ in many cases

There are, though, at least a few regiochemical exceptions....

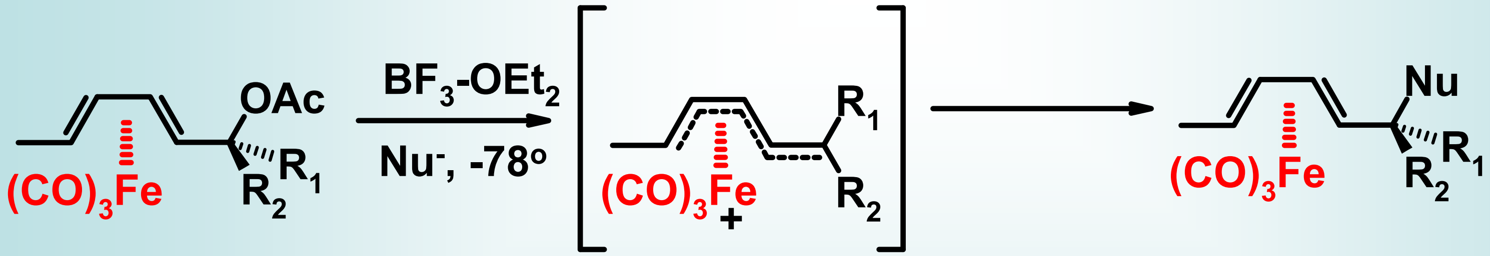


C-2 attack

see Donaldson reviews....most recent..

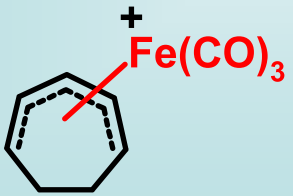
R Donaldson, W. A. *Curr. Org. Chem.* 2000, *4*, 837
R Donaldson, W. A. *Aldrichim. Acta* 1997, *30*, 17

-geometry of pentadienyl thermodynamically prefers a "U" shape, but if it's generated with an "S" shape, it will keep that conformation (configuration?) until about -30°

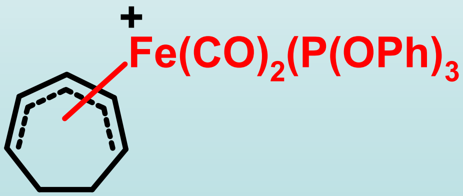


-reacts before isomerization occurs, therefore retention

Uemura, M. et al *Tetrahedron Lett.* 1987, *28*, 641; Roush, W.R. et al *Tetrahedron Lett.* 1994, *35*, 7347 and 7351.



doesn't work;
nucleophiles
deprotonate
instead



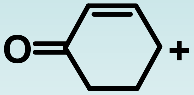
Pearson's solution
-see book

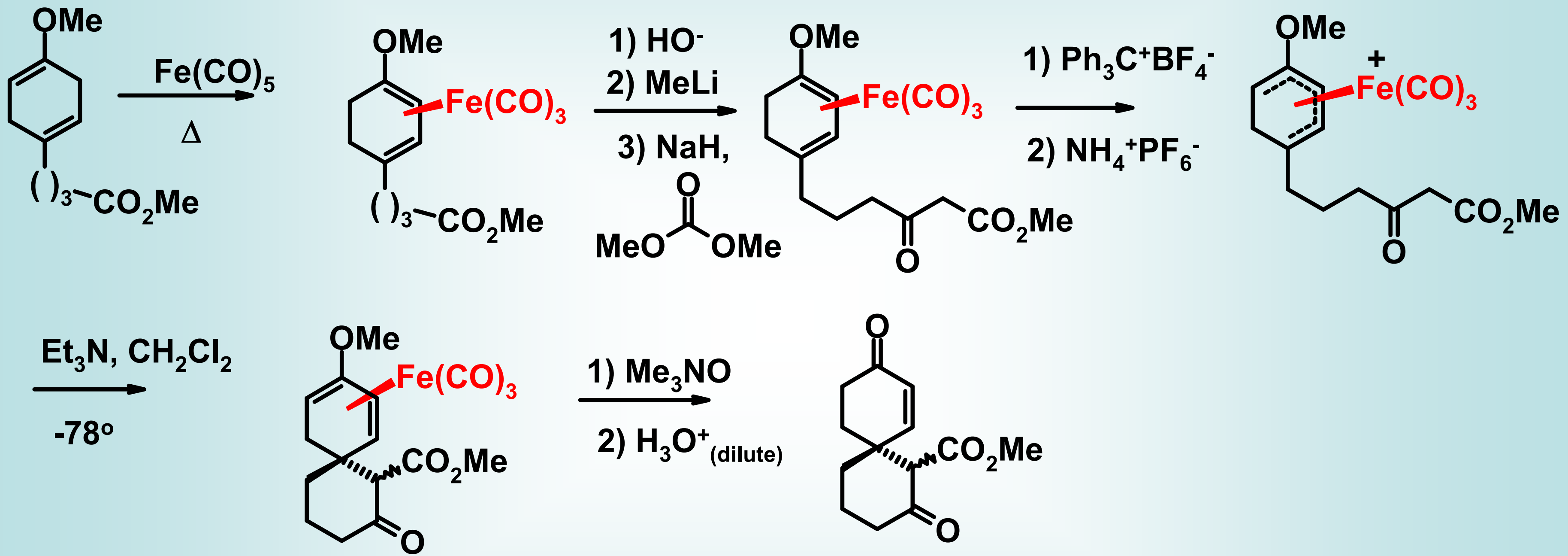
Synthetic Utility

-widely used by Pearson's and Knolker's groups

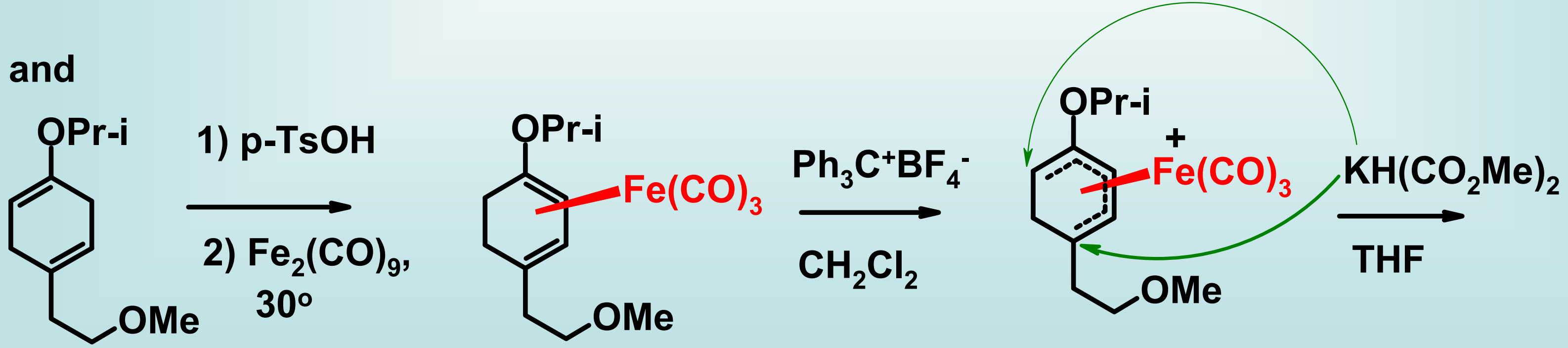
R *Synlett* 1992, 371   R *Chem. Soc. Rev.* 1999, *28*, 151.   R Pearson, A.J. *Acc. Chem. Res.* 1980, *13*, 463.

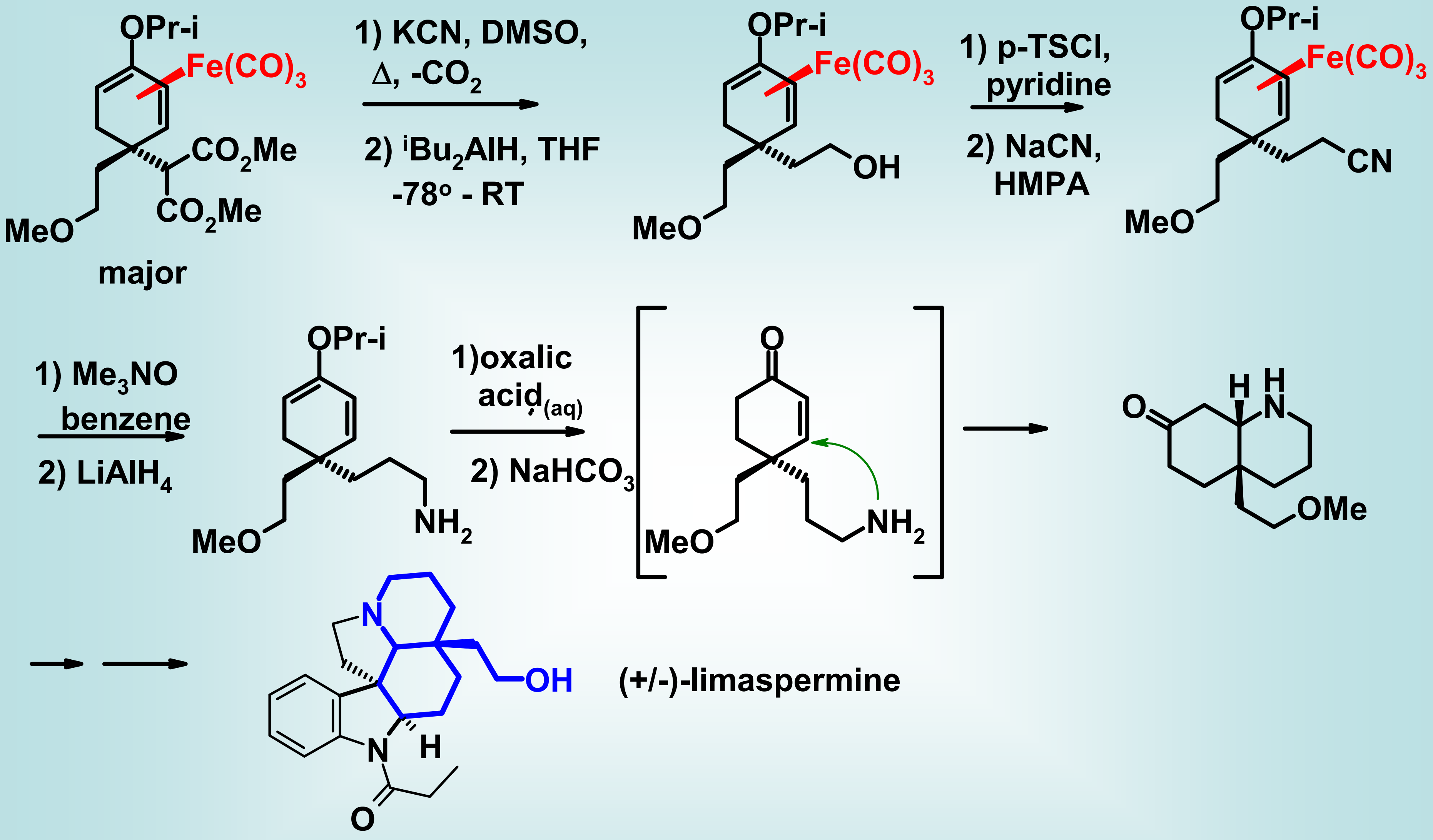
Example: as equivalent of cyclohexenone γ-cation





and

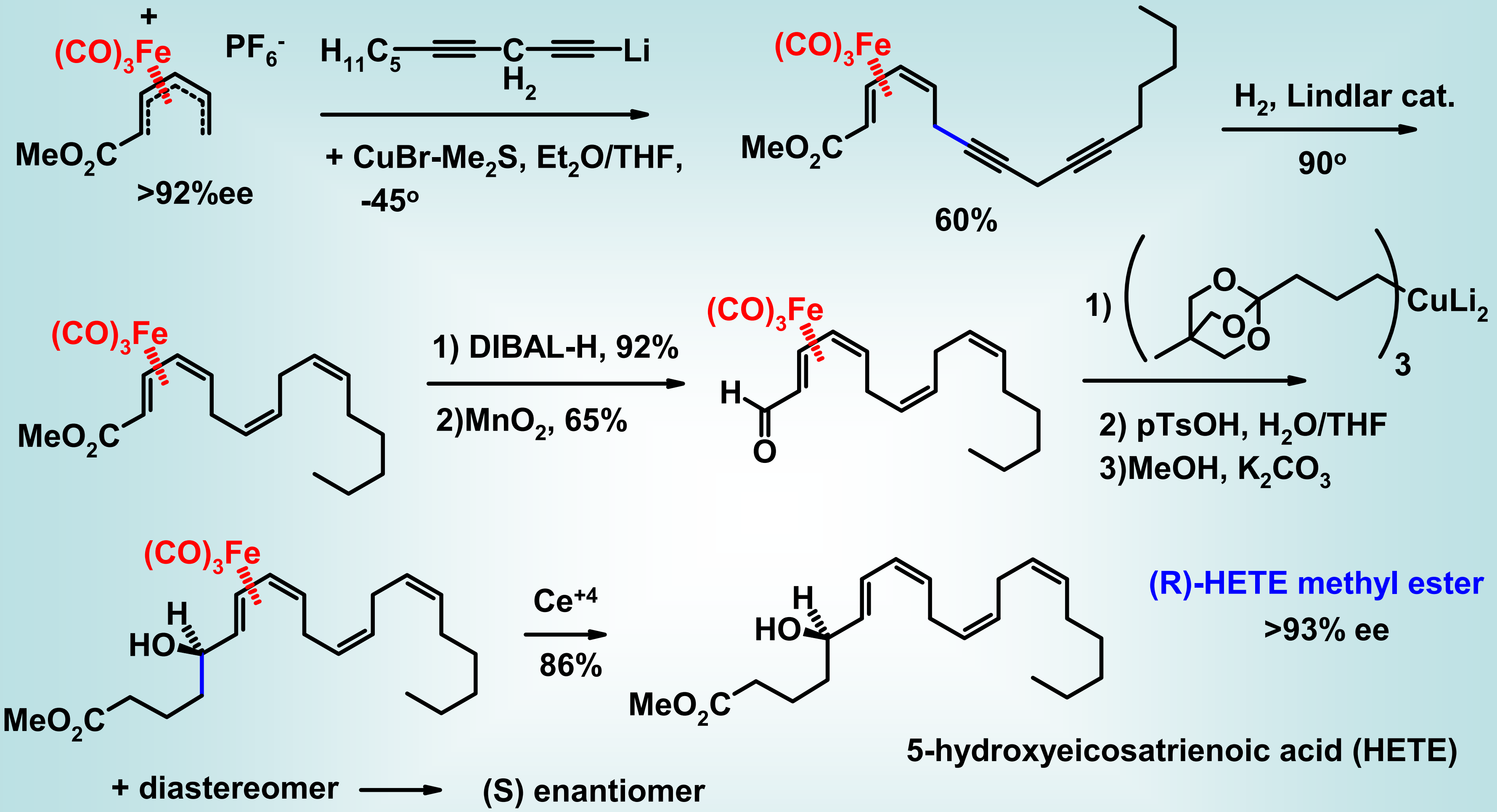




Other Pearson reviews:

R *Science* 1984, *223*, 895; R *Pure Appl. Chem.* 1983, *55*, 1767;
R *Chem. Ind.* 1982, 741; R Knolker, H.J. *Chem. Soc. Rev.* 1999, *28*, 151.

Acyclics - synthesis of 5-HETE methyl ester



Tao, C.; Donaldson, W.A. *J. Org. Chem.* 1993, *58*, 2134.

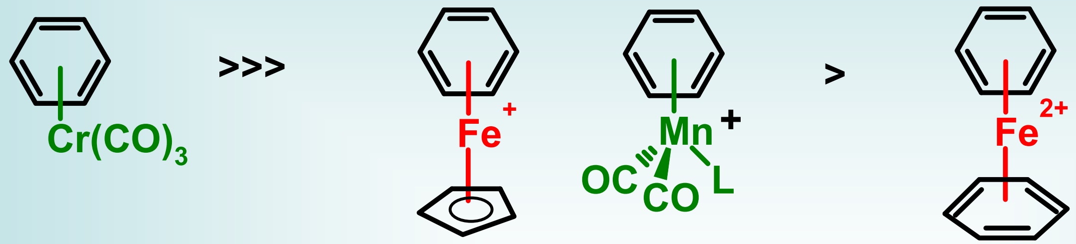
For other metal pentadienyls, see:

R Ernst, R.D. *Chem. Rev.* 1988, *88*, 1255.
R Powell, P. *Adv. Organomet. Chem.* 1986, *26*, 125.

η^6-Triene Metal Complexes

-dominated by h^6-benzene metal complexes
-very extensively developed; many, many complexes known

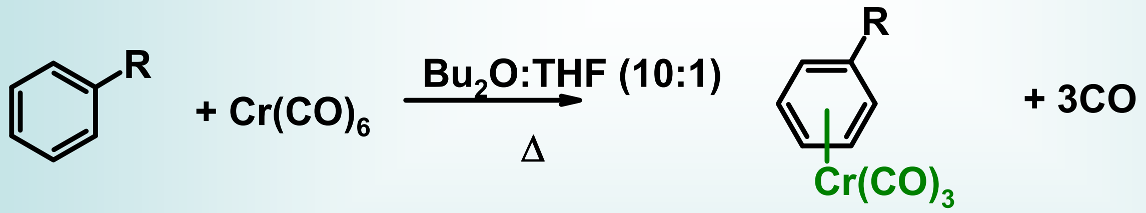
Order of Utility



Preparation of Complexes

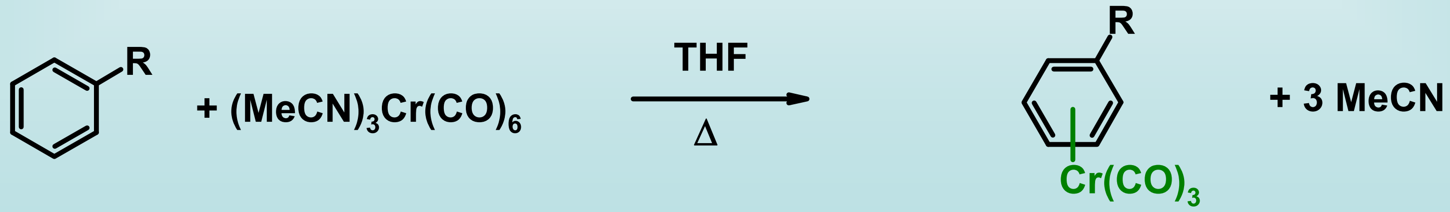
Chromium

a) Standard method - Arene + $Cr(CO)_6$ + heat

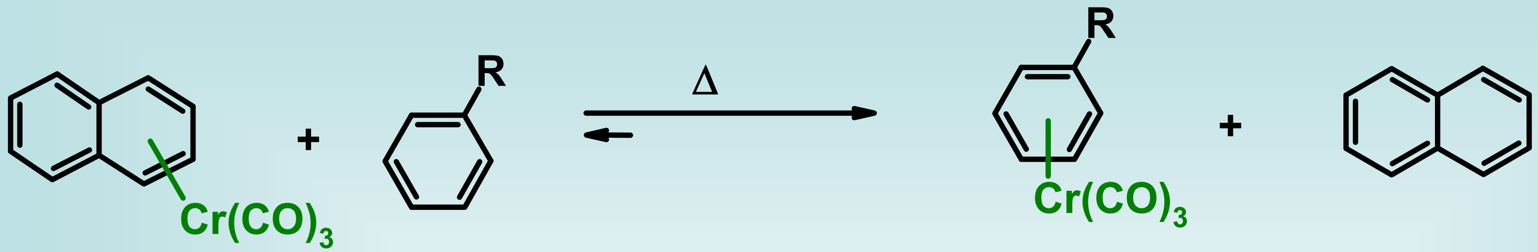


b) milder conditions - arene +$L_3Cr(CO)_3$

L = is often acetonitrile - requires only ca. 70^o



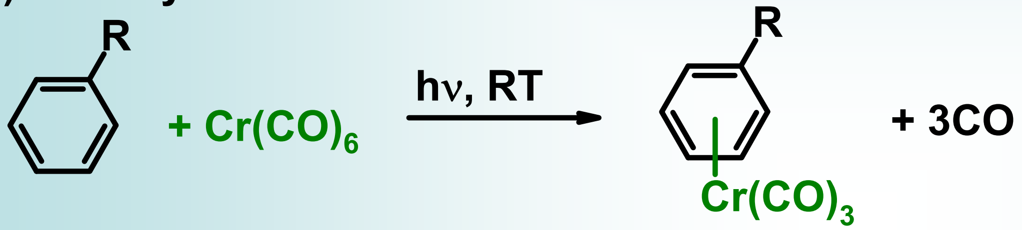
c) by arene exchange - one of the most weakly bound arenes is naphthalene, so



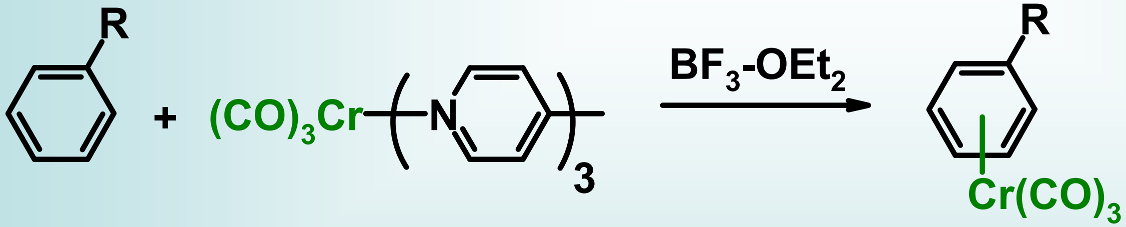
equilibrium is well to the right, normally

Kundig, E.P. et al *J. Organomet.Chem.* 1985, *286*, 183.

d) Photolysis

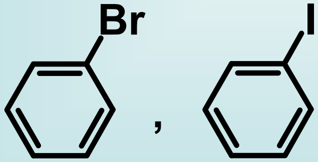


e) last resort, from Cr(CO)(4-picoline)$_3$ + Lewis acid



often works in the most sensitive cases

i.e.,

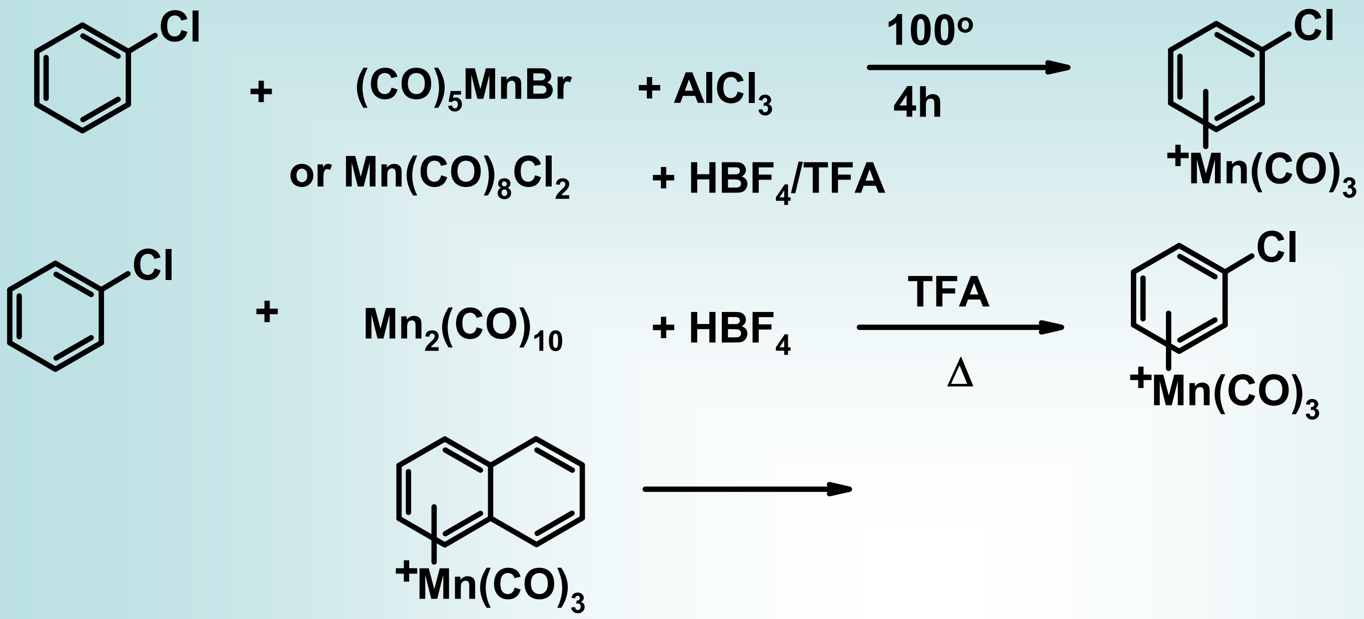


don't work at all under normal conditions, due to oxidative addition

They do complex under these conditions, although the yields are poor

Ofele, K. *Chem. Ber.* 1966, *99*, 1732.

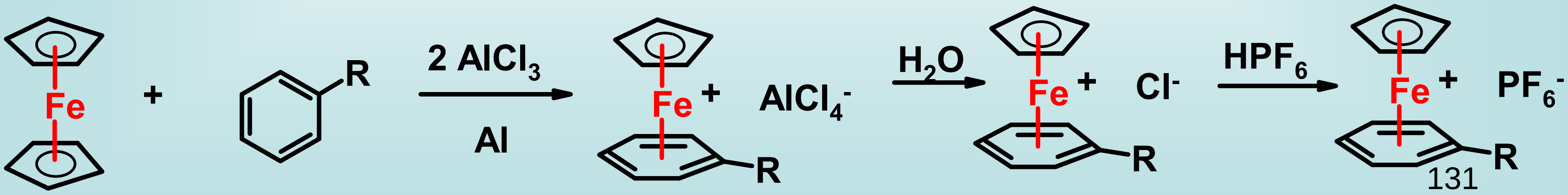
Complexes of Mn



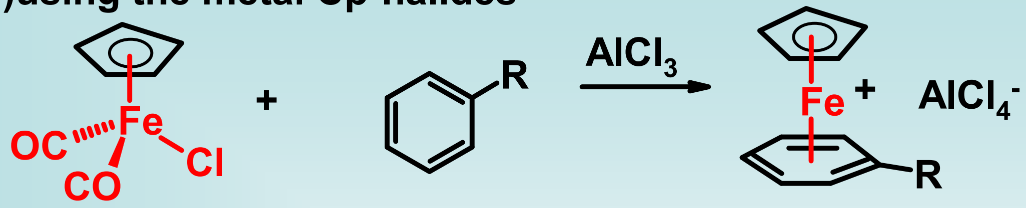
R Sun. S.; Dullaghan, C.A.; Sweigart, D. A. *J. Chem. Soc., Dalton Trans*. 1996, 4493.

Complexes of Iron

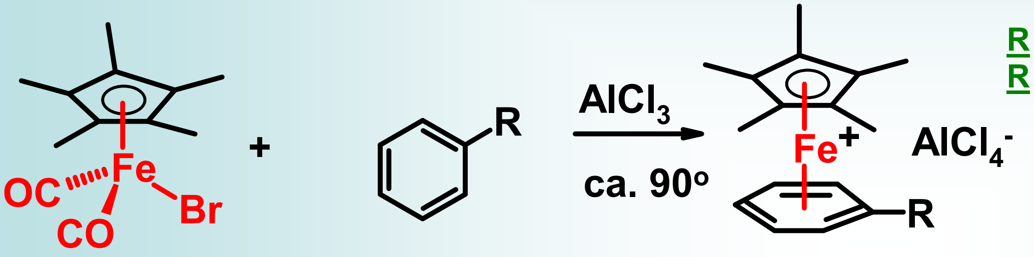
a) Ligand exchange with ferrocene



b)using the metal Cp-halides



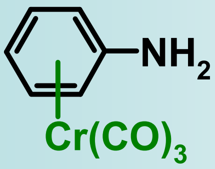
original prep, but not used much any more for Cp complexes
-for Cp* complexes, though, it's the default way



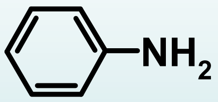
R Astruc, D.*Tetrahedron* 1983, *39*, 4027.
R Kündig, E.P. Top. Organomet. Chem. 2004, 7, 3.

Electronic Effects in η^6-Complexes

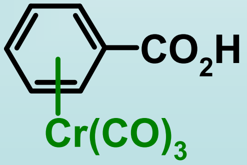
-complexation of the arene by $Cr(CO)_3$ clearly results in a net ***withdrawal*** of π-electron density



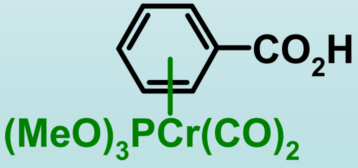
is a weaker base than



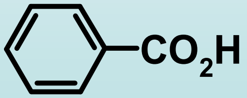
and



pK_a 4.77

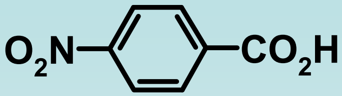


pK_a 5.52



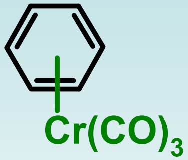
pK_a 5.68

Consider

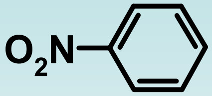


pK_a 4.48

Therefore,



is often considered electronically equal to.......



-this inductive lectron withdrawing ability, as well as resonance electron donating *and* resonance electron withdrawing ability, contributes to the reactions that arene-$Cr(CO)_3$ will undergo

-we will discuss these as we encounter them

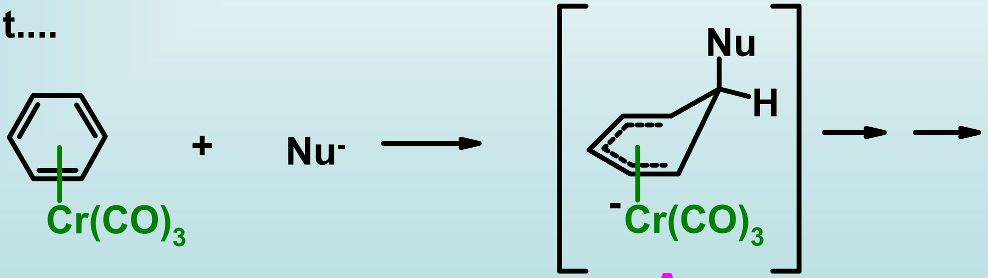
Nucleophilic Additions to Arene-M

R Pape, A.; Kaliappan, K.P.; Kundig, E.P. *Chem. Rev.* 2000, *100*, 2917.
R *Top. Organometal. Chem.* 2004, *7*, Ch.4

background

is not normally a commonly feasible reaction, unless the arene has some strongly electron withdrawing group(s) on it...

But....



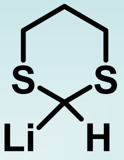
A

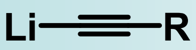
further reaction

is absolutely viable

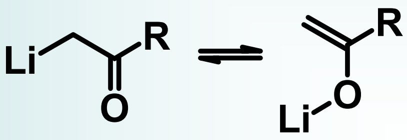
-in 'normal' cases, nucleophiles which work in this process are limited to ones whose conjugate acid (i.e., Nu-H$^+$) has a pK_a > 20

-therefore, successful nucelophiles include...

$LiCH_2CO_2R$, $LiCH_2CN$, $KCH_2CO_2{}^tBu$, LiCHCN(OR), $LiCH_2SPh$, PhLi,  ,

 ,  , ^{t}BuLi

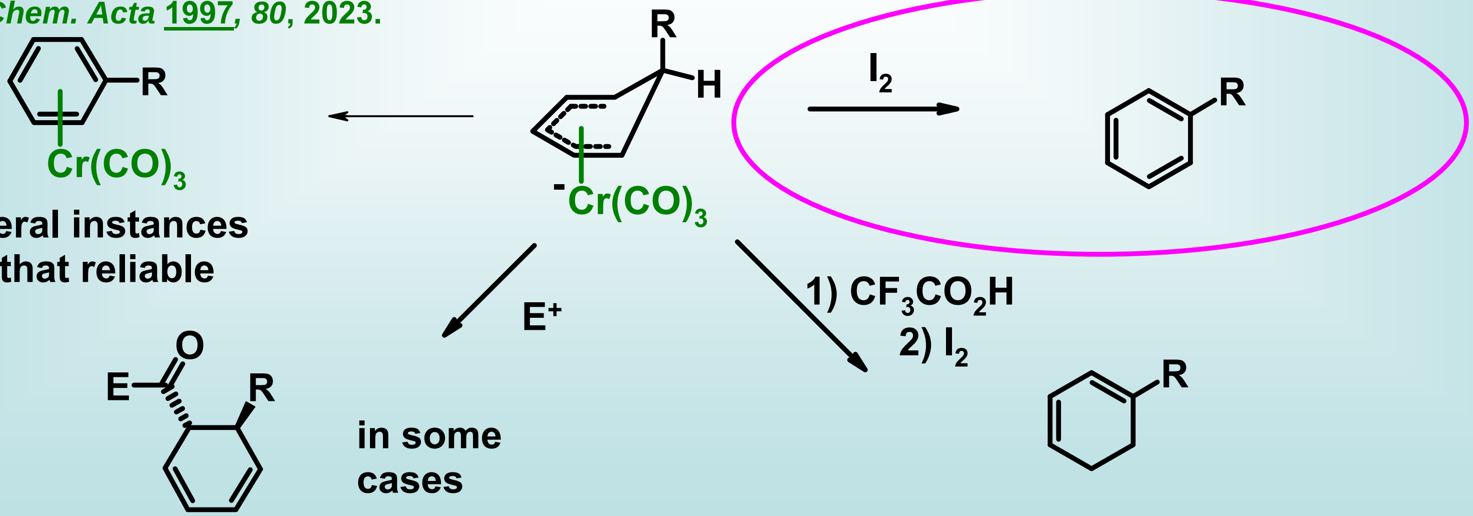
Unsuccessful ones..

$LiCH(CO_2R)_2$,  , Grignards, Me_2CuLi

Note: ^{n}BuLi, MeLi, ^{s}BuLi do *different* reactions

So what does one do with the reaction intermediates, i.e., **A** ?

Chem. Eur. J. 1998, *4*, 251;
Helv. Chem. Acta 1997, *80*, 2023.

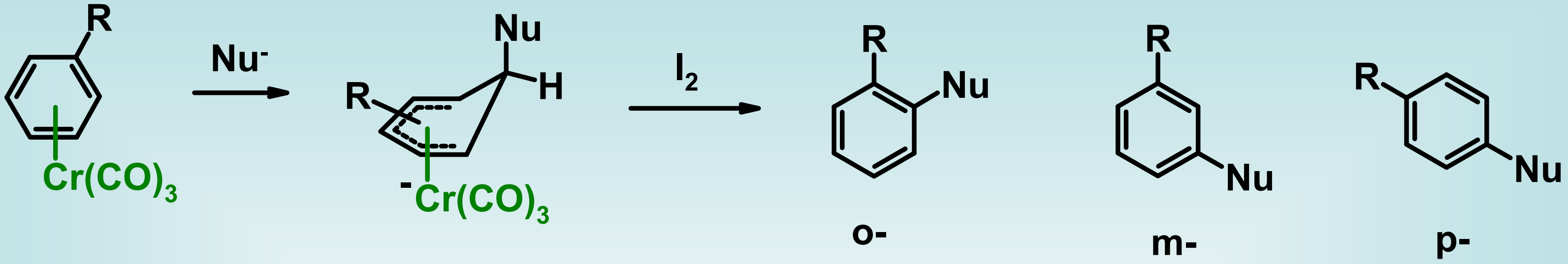


several instances
not that reliable

in some
cases

R Kundig, E.P.; Pape, A. *Top. Organomet. Chem.* 1994, *7*, CH5

Regiochemistry of Nucleophilic Attack

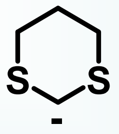


-do get mixtures under these conditions, but the general rules are......

R = electron donating (-OCH$_3$, -CH$_3$, -NMe$_2$)	meta (major)
R = electron donating and large (-SiMe$_3$, -^{t}Bu, -CH(^{t}Bu)$_2$)	para (major)
R = electron withdrawing (i.e, CF$_3$)	para (major)
R = electron withdrawing and coordinating	ortho

-considerable variation with size of nucleophile

-sterically smaller nucleophiles, such as $^-$CH$_2$SPh, give substantial ortho substitution



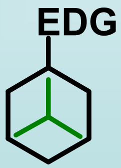
-Note: these are under kinetic conditions (-78^o)

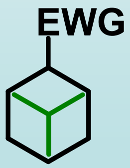
Why this regiochemistry?

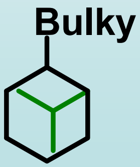
-best guess - a combination of charge and orbital control

-charge control - charge induced by preferred M-CO conformation

-arene C's eclipsed by Cr-CO are attacked preferentially







Frontier Orbital Control

-attack occurs at the lowest unoccupied arene centred M.O. (LUMO)

LUMO coefficients

-the argument is that if there is a good energy match between the LUMO of the arene-$Cr(CO)_3$ and the HOMO of the nucleophile, then orbital control is favoured

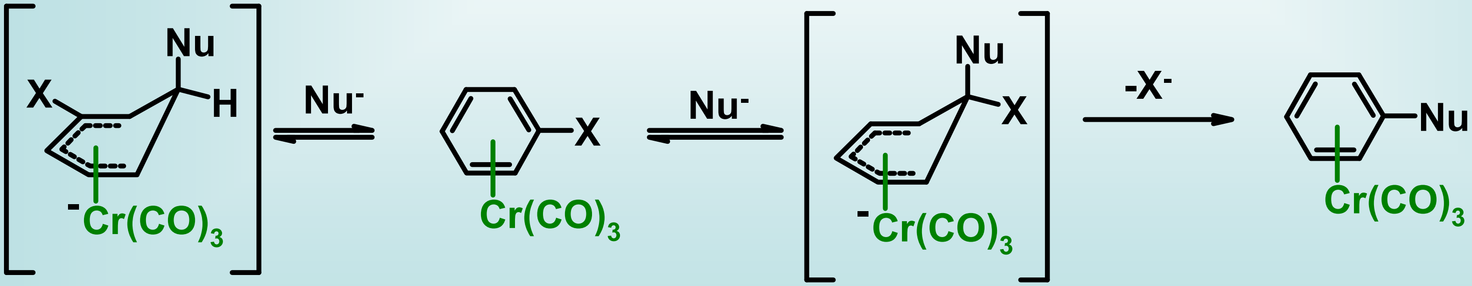
-in the absence of this match, charge control operates

see Semmelhack, M.F. et al *Organometallics* 1983, *2*, 467.

Thermodynamic Control

-it was later realized that this addition to the arene-$Cr(CO)_3$ is reversible in many cases; this has a couple of consequences

1) if there is a leaving group present, one should be able to.....



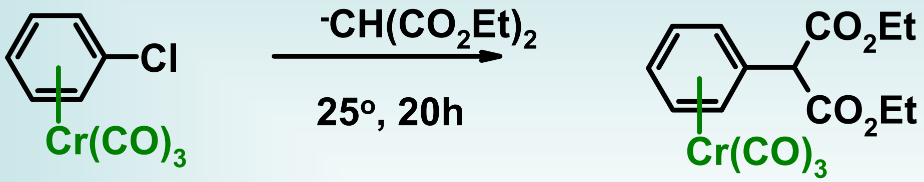
-this is possible, especially for X = F

X = F > Cl, OPh >> others

2) some nucleophiles which don't give noticeable amounts of additionin non-X bearing cases
now work well

i.e, NaOMe,, R_2NH, ^-CN, $^-CH(CO_2Et)_2$ now work

thus

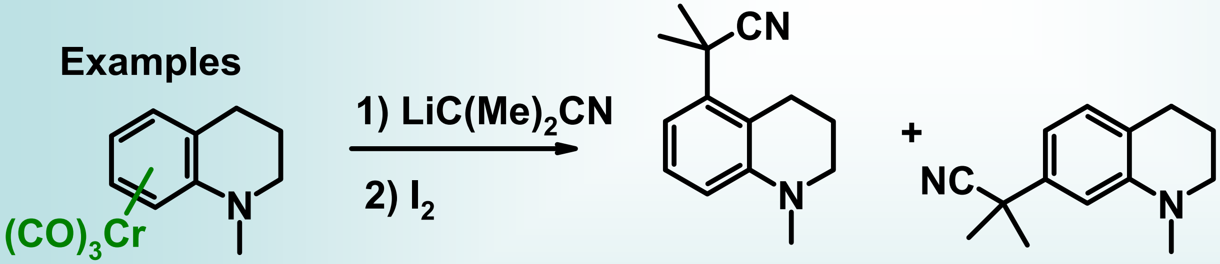


Semmelhack, M.F. et al
J. Am. Chem. Soc. 1974, *96*, 7091, 7092.

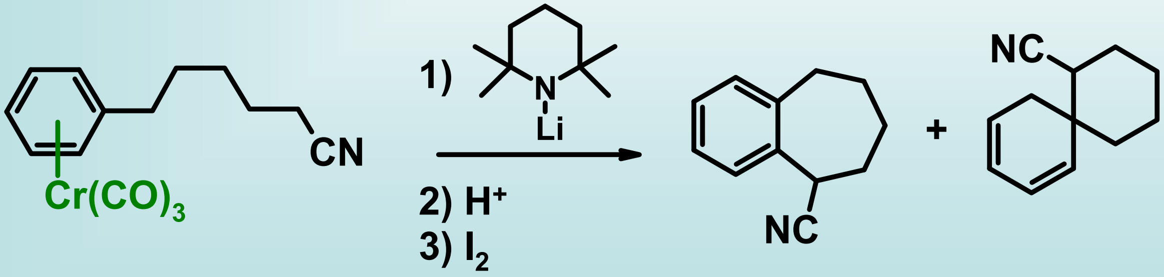
-another consequence

-difference in regiochemistry of addition at different T
-apparent that methoxy still prefers to be *meta*- to nucleophile under thermodynamic conditions
-other substituents are much less predictable

Examples



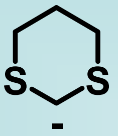
-70°, 1 min 35:64
-70°, 8.6 h 02:97



-78°, THF 72:28
0°, THF 03:97

Semmelhack, M.F. et al *J. Am. Chem. Soc.* 1977, *99*, 959; Ohlsson, B.; Ullenius, C. *J. Organomet. Chem.* 1984, *261*, C34

Note: A couple of nucleophiles that do add kinetically <u>do not</u> undergo reversible reaction

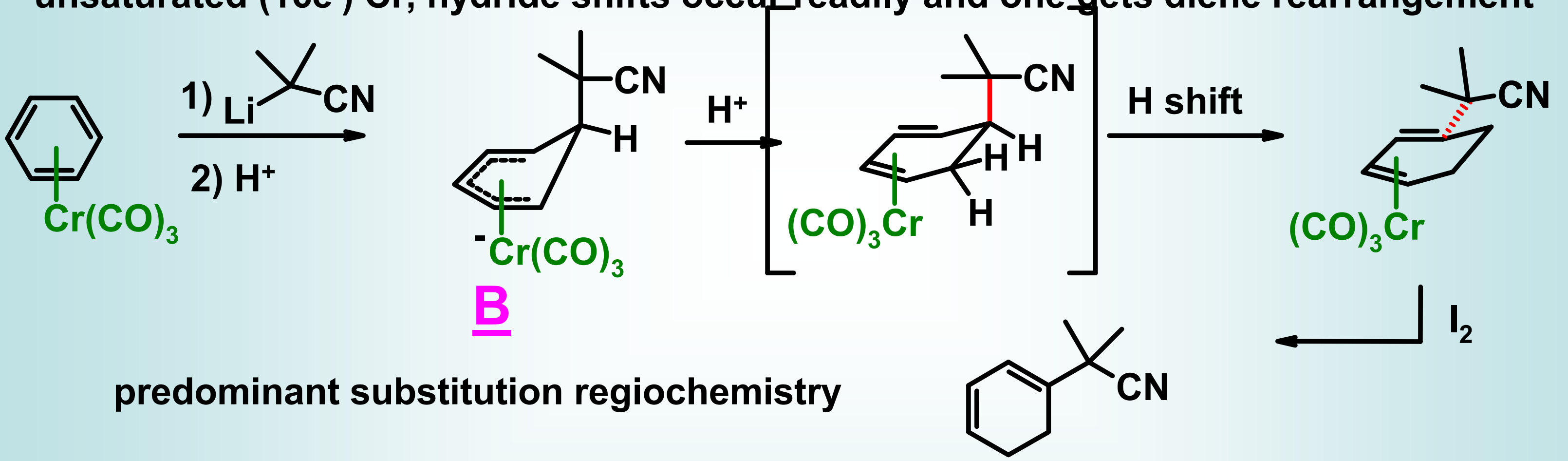


, $^{-}CH_2SPh$, PhLi, ^tBuLi

Kundig, E.P. et al *J. Am. Chem. Soc.* <u>1989</u>, *111*, 1804.
<u>R</u> Kundig, E.P. *Pure Appl. Chem. 1985*, <u>57</u>, 1855.

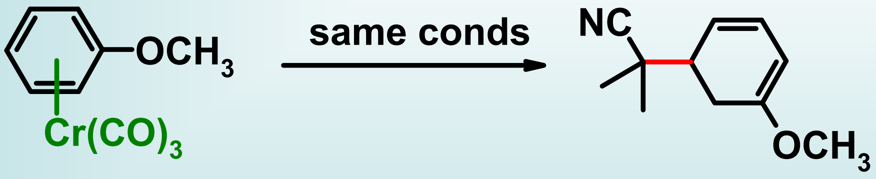
Reaction with protic workup

-if a careful work is done using a proton source instead of I_2, one gets reduced arene complex which then loses Cr easily - since the transient complex is coordinatively unsaturated ($16e^-$) Cr, hydride shifts occur readily and one gets diene rearrangement



predominant substitution regiochemistry

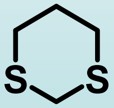
-except



methoxy has very high preference for 1-position

Alkylation of anionic intermediates

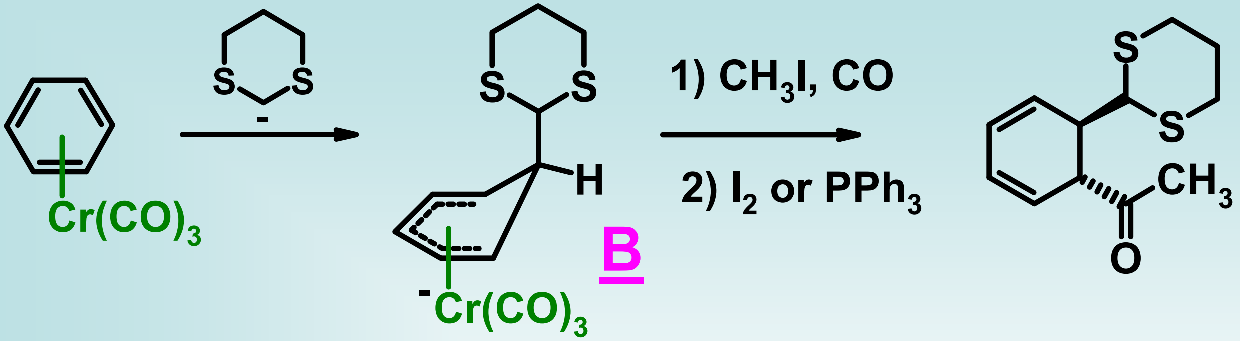
-if the incorporated Nu^- is one of the irreversible ones



, PhLi, ^tBuLi

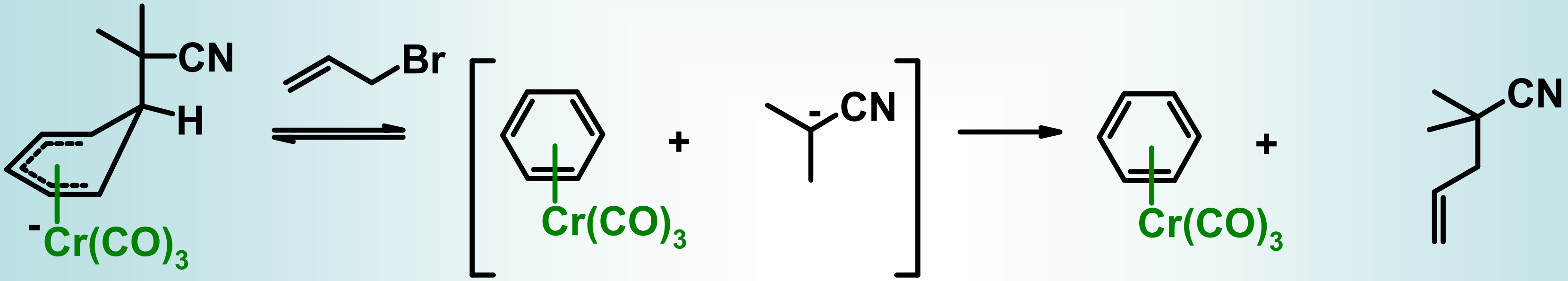
-then the anionic intermediate <u>**B**</u> can be alkylated with 1° alkyl, allylic, benzylic, propargylic iodides, bromides, or sulphonates,

BUT(!), the reaction usually goes with CO insertion (there are exceptions)

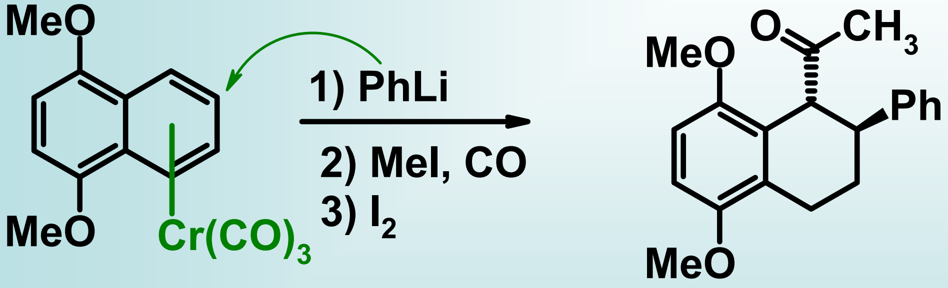


notice stereochemistry
E$^+$ attacks from same side as the metal
-therefore, trans addn

-conversely, nucleophiles which add reversibly fail



-another successful example

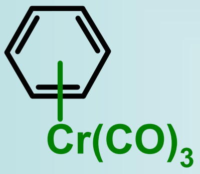


Kundig, E.P. *J. Org. Chem.* 1994, *59*, 4773.
***Top. Organomet. Chem.* 2004, *7*, ch 5**

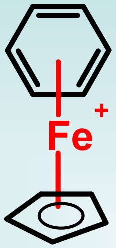
Improving Reactivity - Other Metals

-definite limits on the nucelophilic attack on arene-Cr(CO)$_3$
-therefore, there is some use for other, more electrophilic, M-arene complexes here

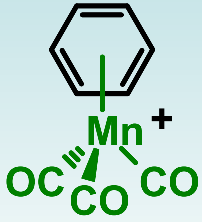
The relative rates of reaction of many of the complexes are known



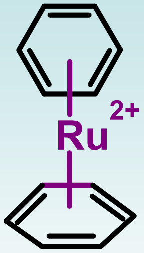
v. small



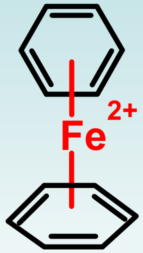
1



11,000

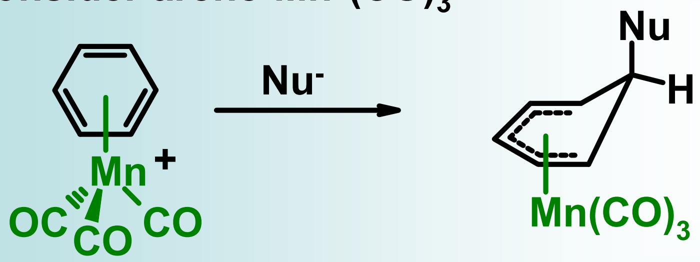


6×10^6

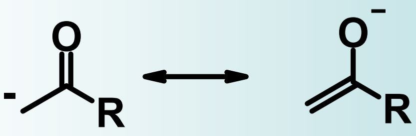


2×10^8

Consider arene-$Mn^+(CO)_3$

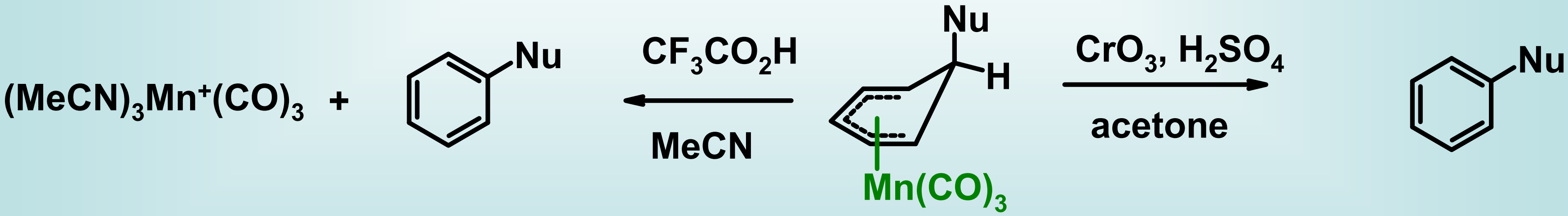


Nu$^-$ = MeLi, PhLi, RMgBr, H$^-$,
$NaCH(CO_2Et)_2$,



Note: $^-$CN and :PPh_3 add, but are reversible

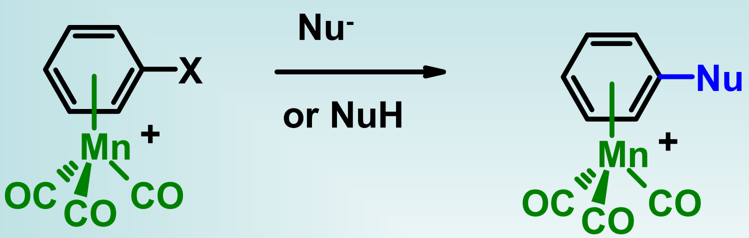
-so what now?



-other chemistry is possible with the intermediate dienyls, but it's beyond the scope of the course

R Pike, R. D.; Sweigart, D.A. *Synlett* 1990, 565; *J. Chem. Soc. Dalton Trans* 1996, 4493.

-and if there is a leaving group on the arene, the concept is the same, but the reversible nucleophiles are a different group



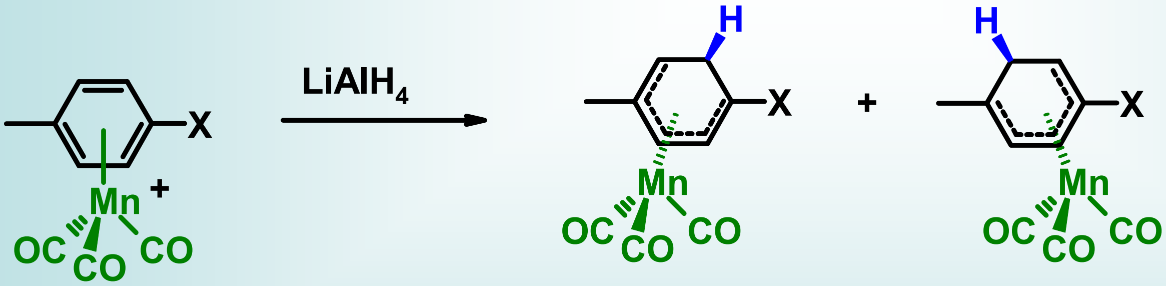
X = Cl, Br, F

-nucleophiles which can add reversibly and therefore do this include
MeO^-, PhO^-, PhS^-, N_3^-, R_2NH

but not H^-, R^-, Ph^-

-the regiochemistry of kinetic substitutions are not as thoroughly studied, but what's available shows the same general trends

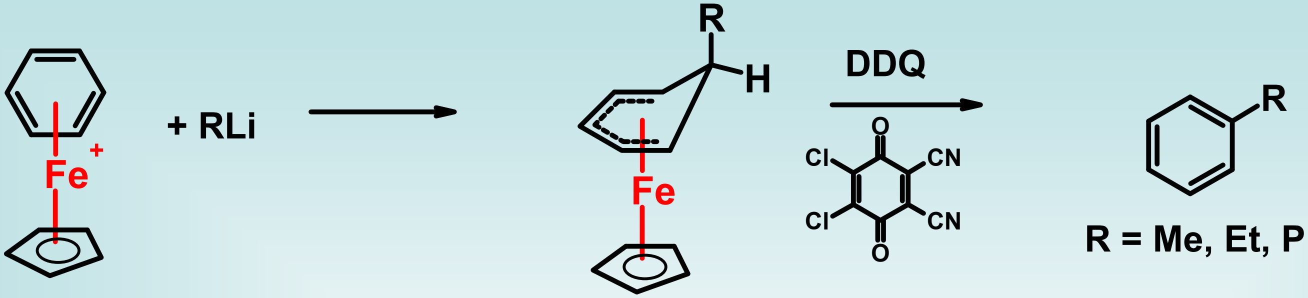
i.e., EWG directs *ortho*- attack (para is usually blocked in Mn studies)
EDG directs *meta*- attack



X = Cl 69:37
X = NMe_2 3:97

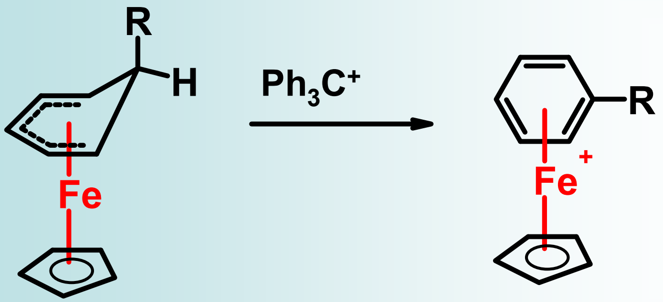
Pauson, P.L. et al *J. Chem. Soc., Dalton Trans.* 1975, 1677 and 1683
Kane-Maguire, L.A.P.; Sweigart, D.A. *Inorg. Chem.* 1979, *48*, 700.
Pearson, A.J. *Tetrahedron* 1992, *48*, 7527
J. Org. Chem. 1991, *56*, 7092.

And the Cp-Fe$^+$-arenes?

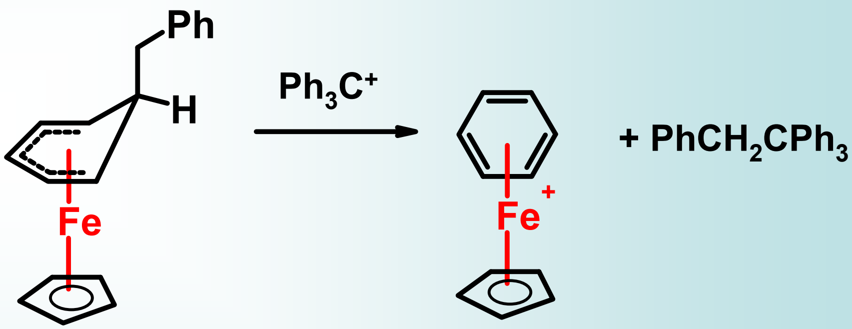


R = Me, Et, Ph, $PhCH_2MgBr$

-here, there are more examples of successful examples of hydride abstraction to get back the complex

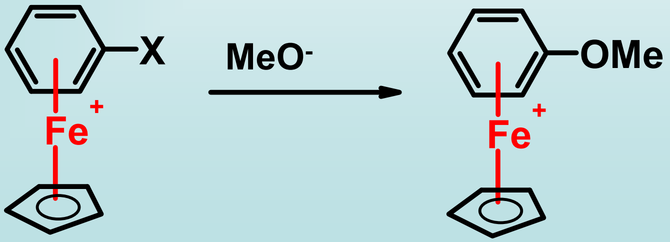


with the exception of benzyl



R Astruc, D. *Tetrahedron* 1983, *39*, 4027.
R Adb-El Aziz, A.S.; Bernardin, S. *Chem. Soc. Rev.* 2000, *203*, 219.

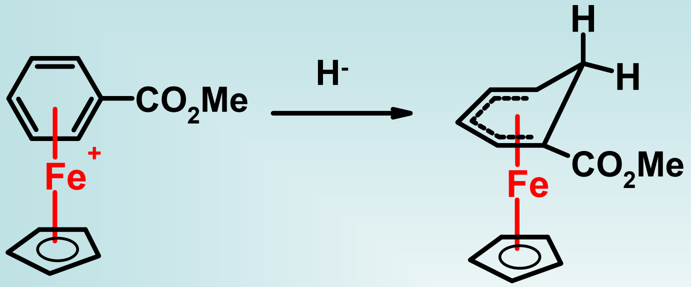
A similar reaction pattern for substitutions are observed with the haloarenes



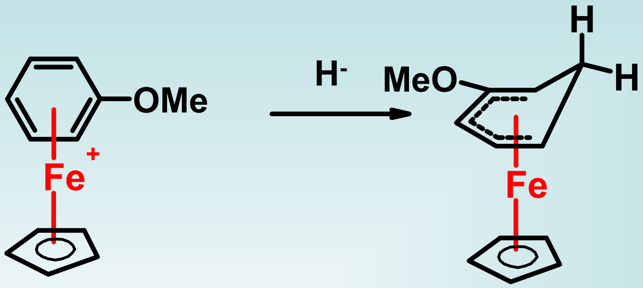
Nu^- = PhO^-, RO^-, RS^-, R_2NH, $NaCH(EWG)_2$

-fairly analogous trend is seen in the kinetic regiochemistry

EWG - ortho attack

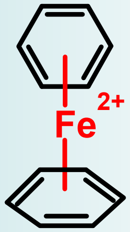


EDG - meta attack



McGreer, J . F.; Watts, W.E. *J. Organomet. Chem.* 1976, *110*, 103
Clack, D.W.; Kane-Maguire, L.A.P. *J. Organomet. Chem.* 1979, *174*, 199.

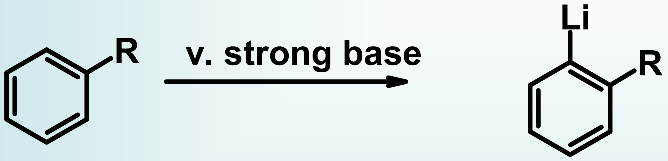
Reactions on



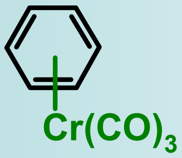
are very similar
-see Astruc review if interested

Effect #2 of electron withdrawing effect of arene-Cr(CO)$_3$
-enahanced acidity of arene ring protons

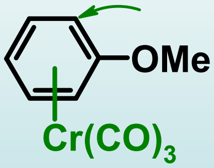
Consider



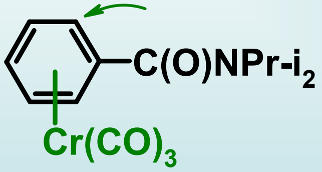
reaction is feasible, but.....pK$_a$'s are 38-42
the pK$_a$'s of arene-Cr(CO)$_3$ are
6-7 pK$_a$ units more acidic



pK$_a$ = 34.8

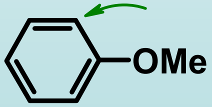


pK$_a$ = 33.0

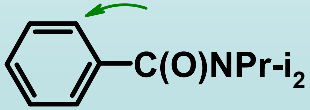


pK$_a$ = 31.1

pK$_a$ = 41.2



pK$_a$ = 39.0



pK$_a$ = 37.8

pK_a associated with LDA is 35.7; LiTMP 37.1, so these can now be used as bases

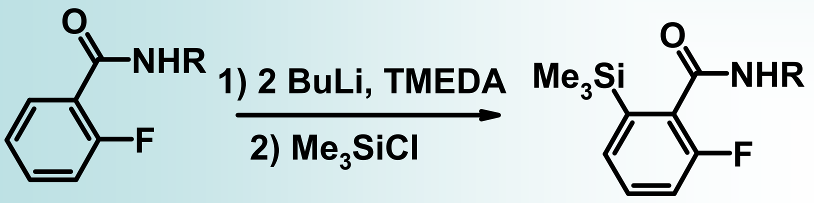
-excellent for *ortho-* functionalization of aromatics; and

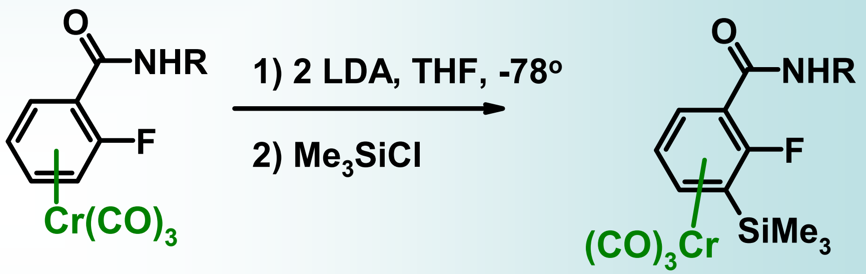
-one gets a change in some of the relative abilities to direct *ortho-* lithiation

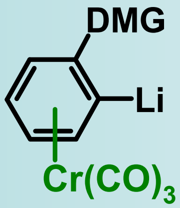
for free arene $-CONR_2 > -SO_2NR_2 > -NHCOR > -CH_2NR_2 > -OMe > -NR_2 = -F$

for Cr complexes $-F > -C(O)NHR > -CH_2NR_2 = -OMe >> -CH_2OMe > -NR_2, -SR$

So

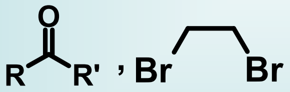




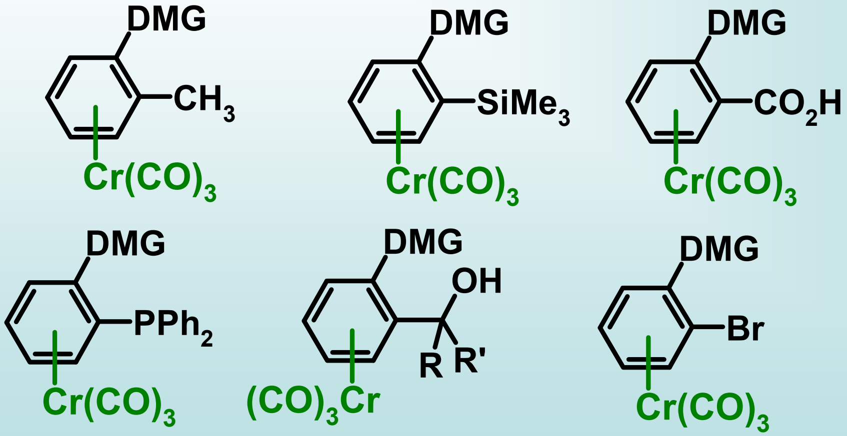


can be trapped by a wide range of E^+

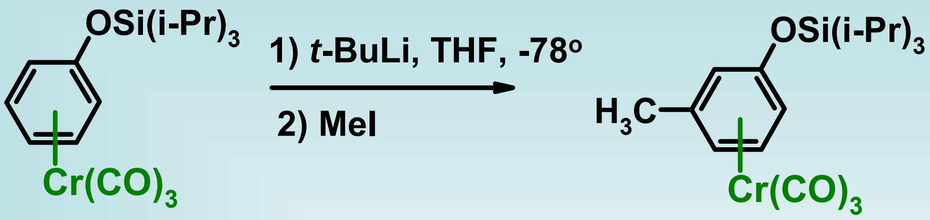
CH_3I, Me_3SiCl, CO_2, Ph_2PCl,



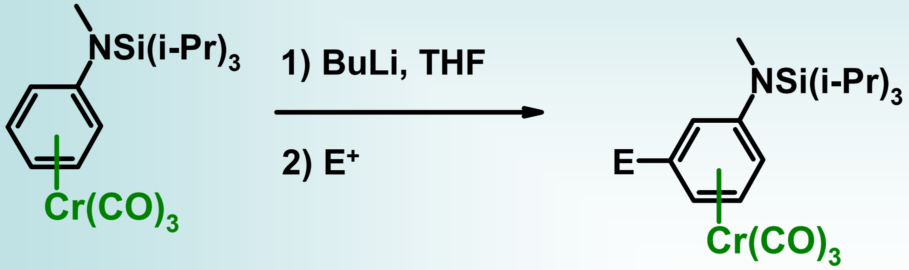
to give



further



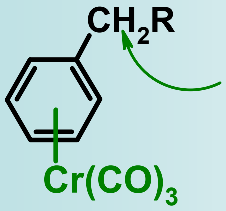
this **meta** metallation is unheard of in chemistry of free arenes



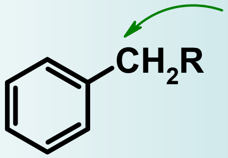
Widdowson, D.A. *J. Chem. Soc., Chem. Commun.* 1983, 955.
Fukui, M., et al *Tetrahedron Lett.* 1982, *23*, 1605.

most recent review: R Semmelhack, M. F.; Chlenov, A. *Top. Organomet. Chem.* 2004, *7*, CH 3

Effect #3 of $Cr(CO)_3$ on arenes



benzylic site also has enhanced acidity relative to

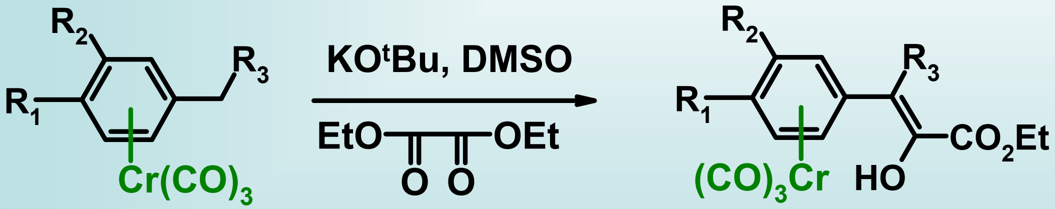


pK_a ca. 40

-so benzylic deprotonation is quite easy

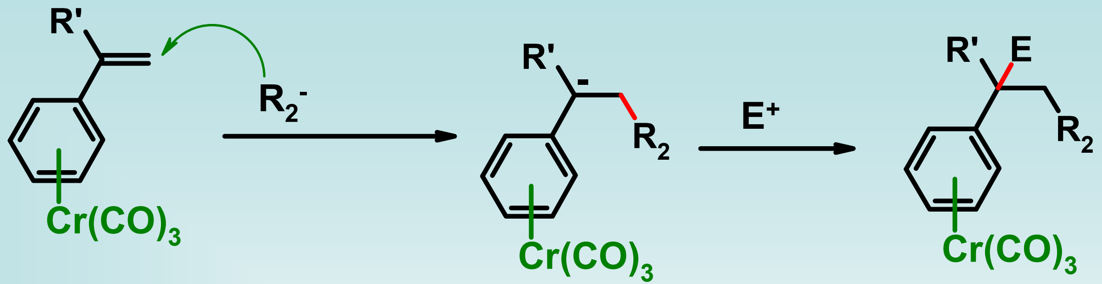
-never seen pK_a measured by I guess it's about 25

-as a result, one can often do benzylic deprotonation reactions which fail with the free arene

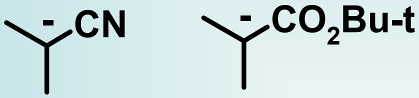


Jaouen, G. et al
J. Chem. Soc. Chem. Commun. 1984, 602, 475
J. Chem. Soc. Chem. Commun. 1981, 1264
J. Organomet. Chem. 1984, *102*, C37.

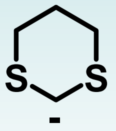
R_1, R_2, R_3 not acidifying groups
(i.e., H, simple alkyl)



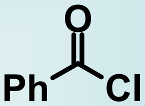
R_2 =



, ^{n}Bu$^-$, Ph$^-$,



E^+ = H^+, CH_3I,



Semmelhack, M. F. Seufert, W.; Keller, L. *J. Am. Chem. Soc.* 1980, *102*, 6586.
Uemura, M.;Minami, T.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* 1984, 1193.

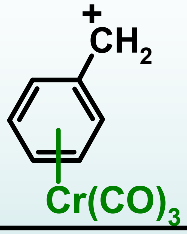
-appears to be both a kinetic and a thermodynamic effect

R Davies, S. G. et al *Adv. Met. Org. Chem.* 1991, *2*, 1.

Effect #4 Stabilization of Benzylic Cations

-recall our discussion of pK_{R+} values....

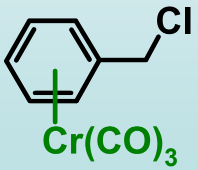
$PhCH_2^+$ < -17.3 Ph_2CH^+ -13.4



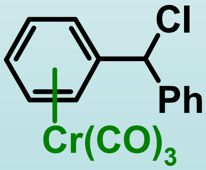
-11.8 Ph_3C^+ -6.6

less stable → more stable

also, the S_N1 solvolyses of

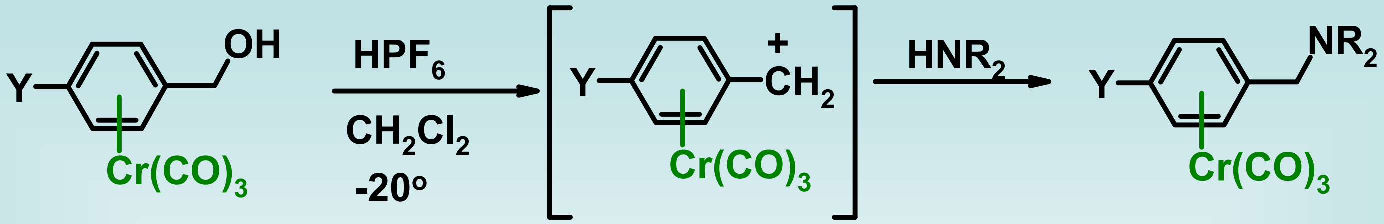


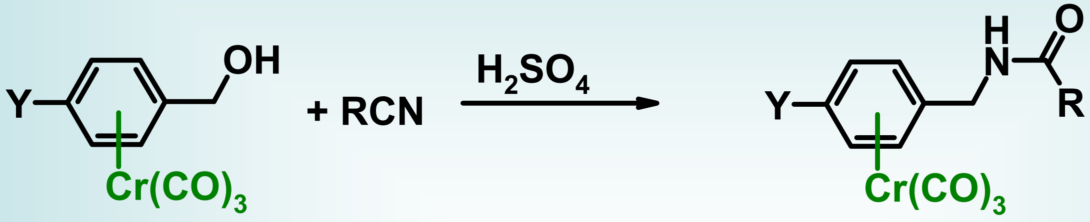
and



are 10^3 - 10^5 times faster than the corresponding non-complexed arenes

-makes the following reactions possible



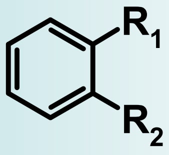


-this Ritter reaction only works with 3^o benzylic halides

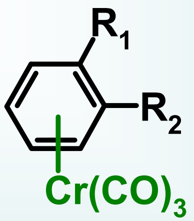
R Davies, S.G. *Synlett* 1993, 323.

Other Effests in $Cr(CO)_3$-Arene Complexes

-stereochemistry



is flat, achiral
σ- plane of symmetry

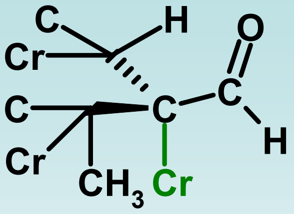


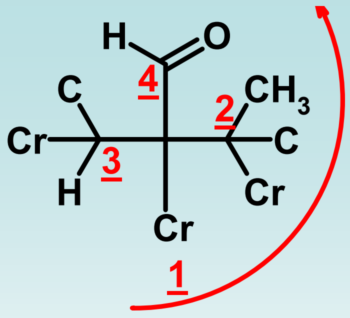
σ- plane is gone
Chiral

-so what is R- and what is S- ??

Consider

-at position 1 we have

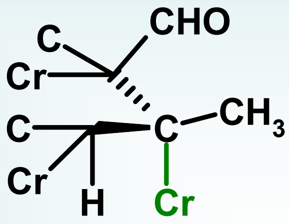


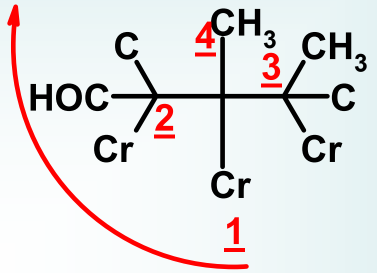


counterclockwise

-therefore,
(S)-enantiomer

-at position 2 we have





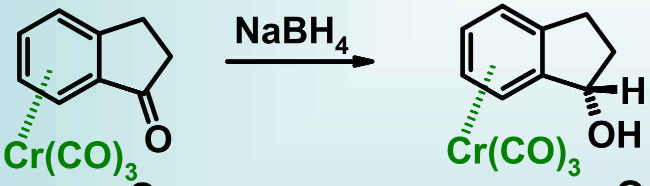
clockwise

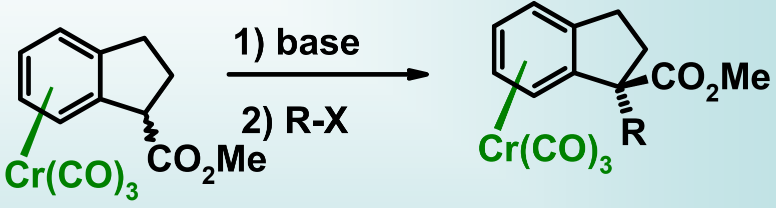
-therfore,
(R)-enantiomer

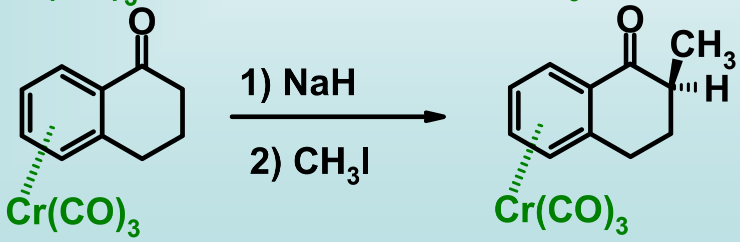
-this is (1S,2R)-2-methylbenzaldehyde chromium tricarbonyl

Note: Davies just uses the label at position 1, as the 2-position is then defined automatically

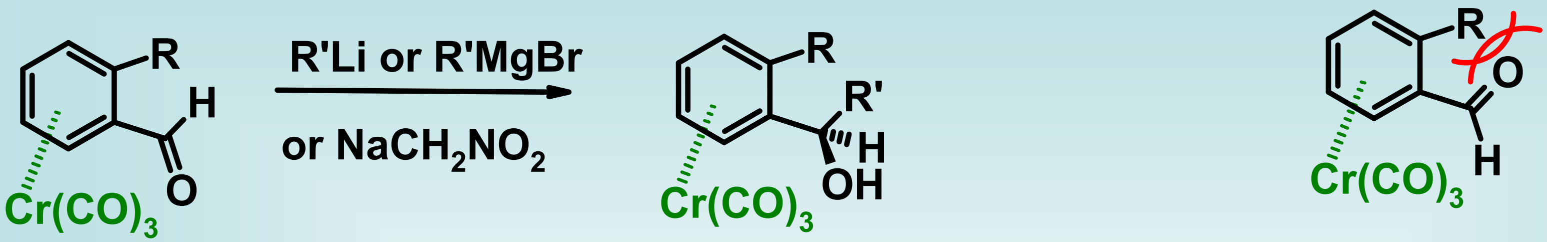
-chiral centre (or plane); therfore should be able to do asymmetric reactions
-will give a sampling, as this is a fairly new and developing area



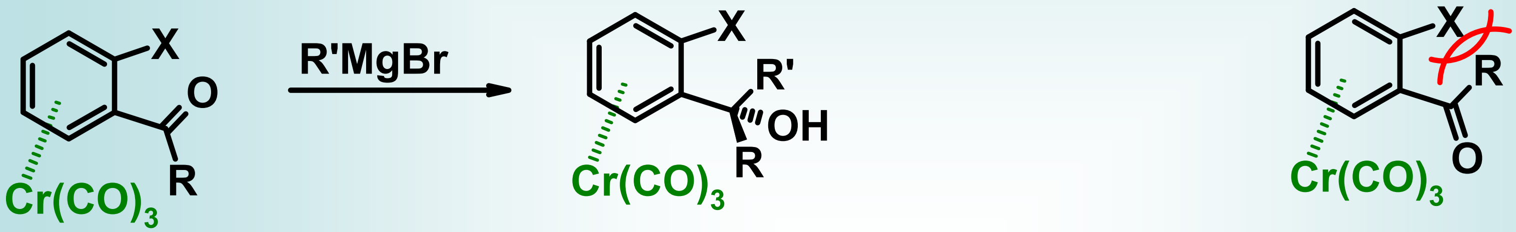




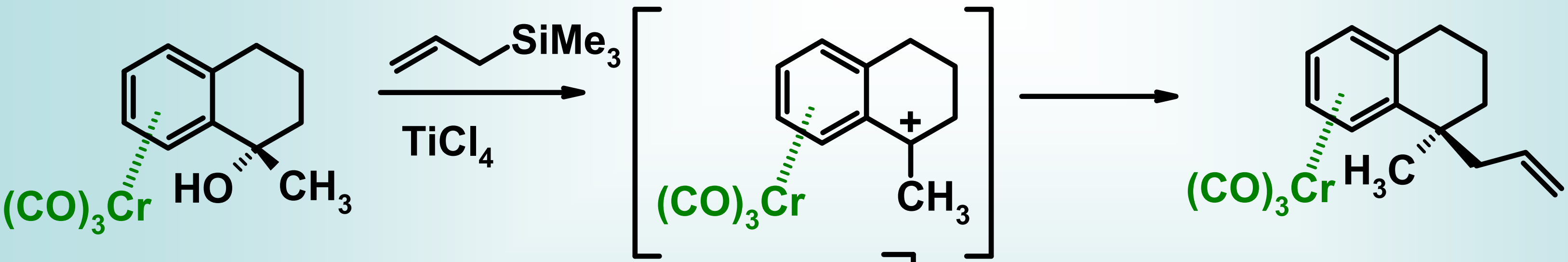
Acyclic cases

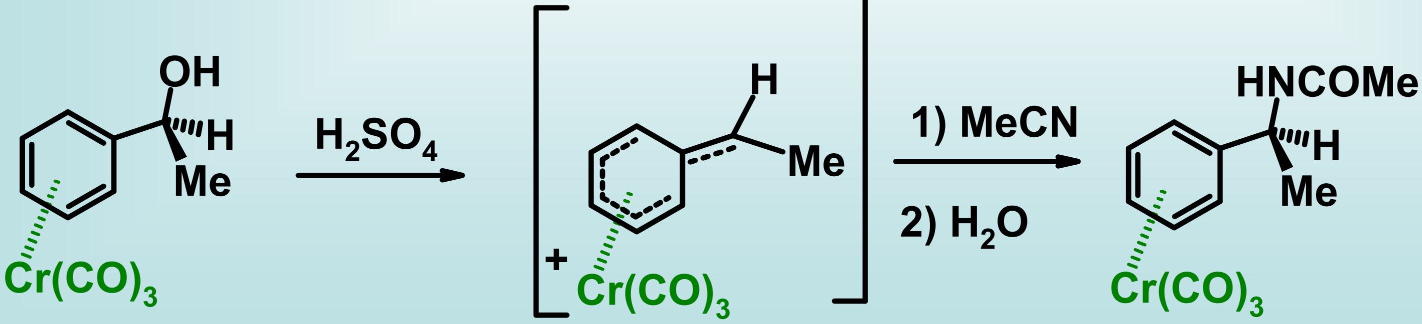


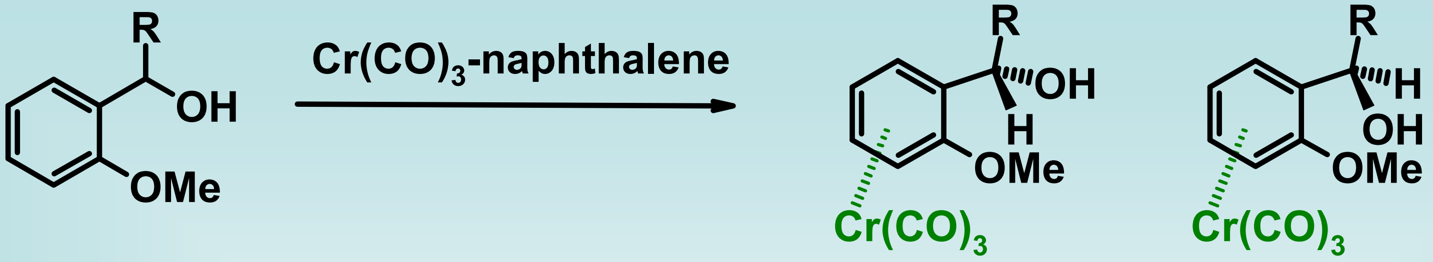
disfavoured rotamer



X = CH$_3$, OR$_2$ R = Me, Et, alkyl

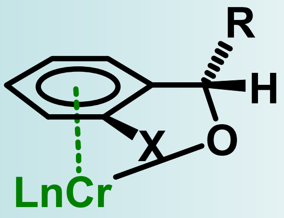




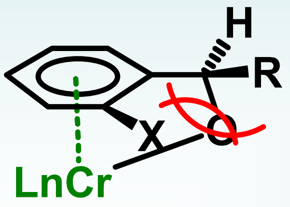


major

because



favoured

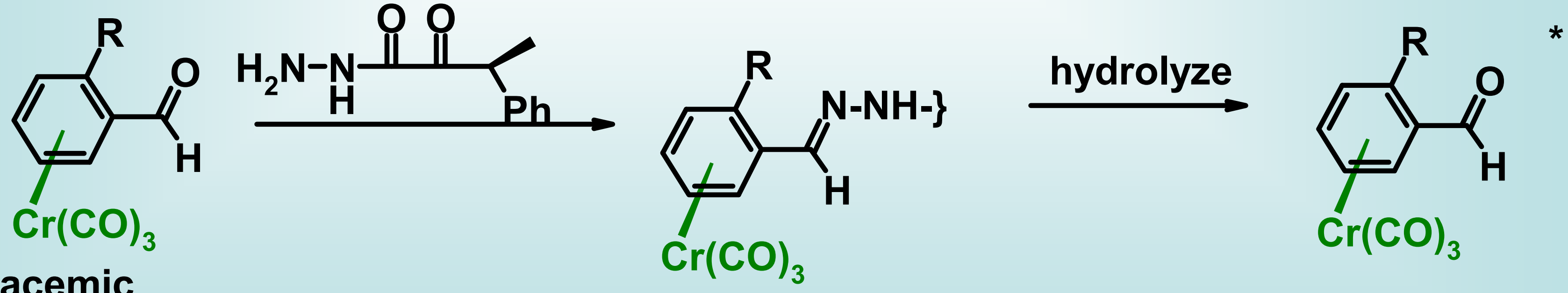


disfavoured

R Solladie-Cavallo, A. *Adv. Met.-Org. Chem.* 1989, *1*, 99.
R Uemura, M. Adv. Met.-Org. Chem. 1991, *2*, 99.
R Davies, S. et al *Adv. Met.-Org. Chem.* 1991, *2*, 1.

-many of these are done on racemic material
-so how does one get enantiomerically pure complexes?

1)



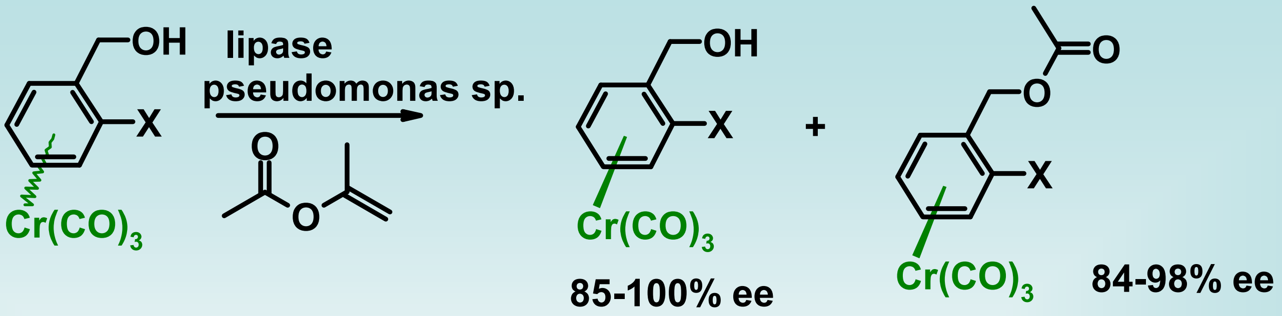
racemic

separate diastereomers

enantomerically pure

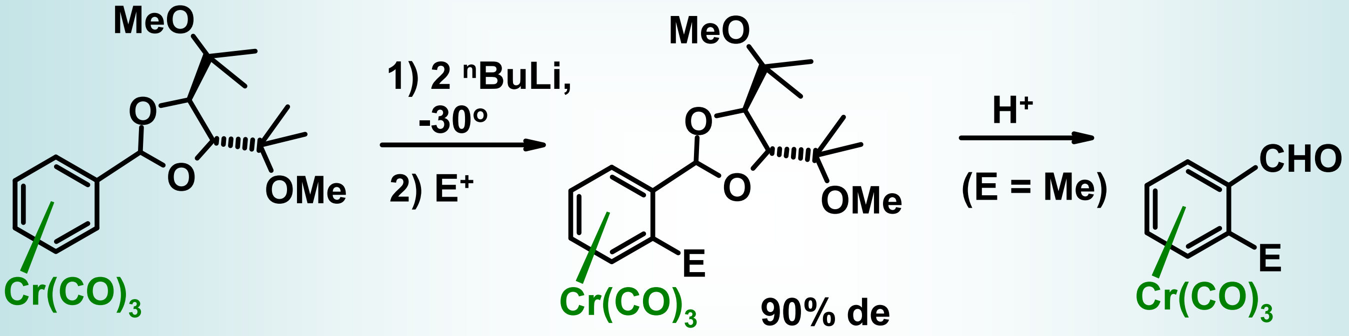
Classical Resolution

2) kinetic resolution



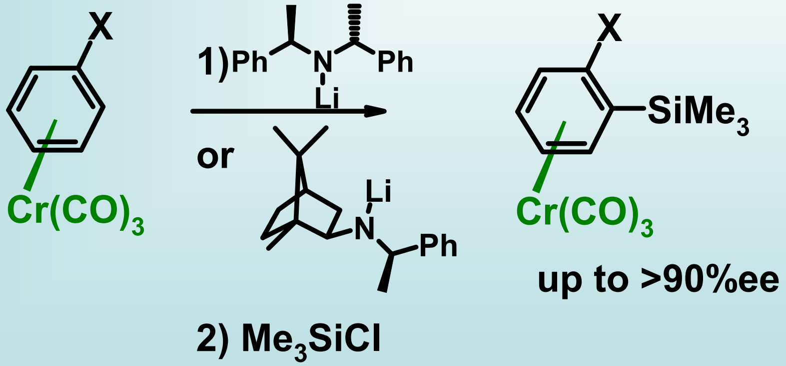
Uemura, M. et al *Tetrahedron Lett.* 1990, *31*, 3603; Jaouen, G. et al *J. Chem. Soc., Chem. Commun.* 1984, 1284.

3) chiral auxiliaries



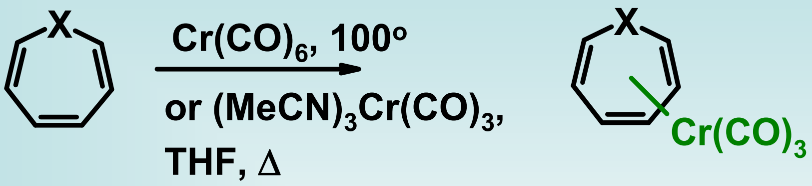
Kondo, Y.; Green, J.R.; Ho, J. *J. Org. Chem.* 1993, *58*, 6182.

4) enantioselective functionalization



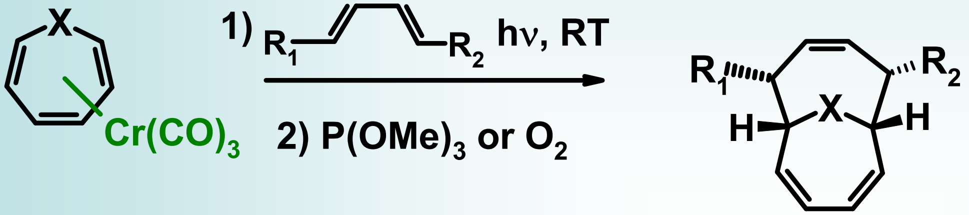
Kundig,E.P. at al *Tetrahedron Lett.* 1994, *35*, 3497
Simpkins, N.S. et al *J. Org. Chem.* 1994, *59*, 1961
Siwek, M.J.; Green, J.R. *J. Chem. Soc., Chem. Commun,* 1996, 2359.

Other η^6-Cycloalkatriene-Cr(CO)$_3$ Complexes



X = N-CO_2Me, C=O, SO_2, CH_2, CH(Me)

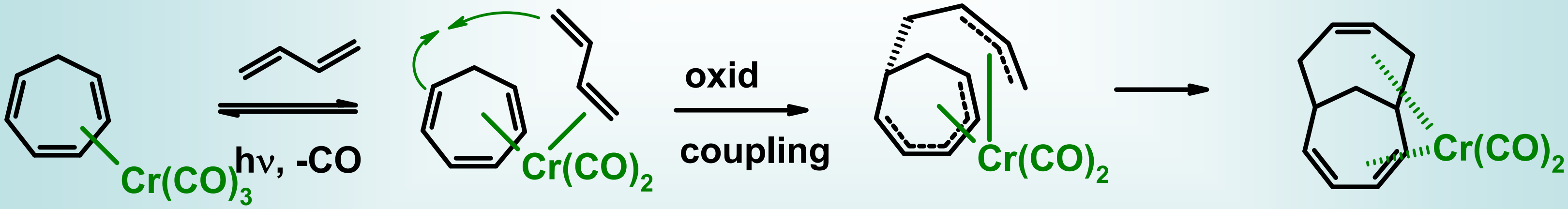
unlike Fe complexes, this is η^6



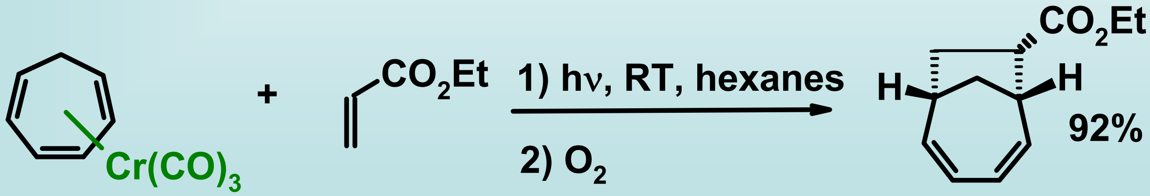
[6+4] cycloaddition
good yields

Notes: rates unchanged if R's = EWG or EDG
-if there are substituents on remote sites of triene, regiochemistry is 1:1

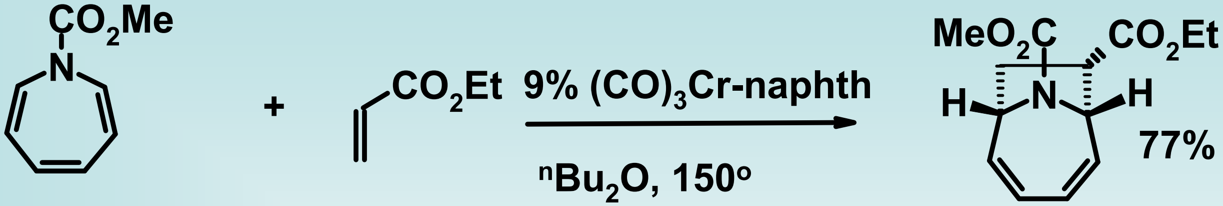
Mechanism(?) - not concerted



-this is stepwise in nature, so there is no 'concertedness' reason why the [6+2] should fail, so...



-both of these can be catalytic in Cr - often in the presence of Mg°



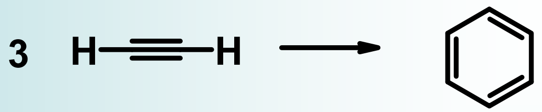
R Rigby, J.H. *Adv. Met-Org. Chem.* 1985, *4*, 89.
R Rigby, J.H. *Tetrahedron* 1999, *55*, 4251.
R Rigby, J.H. *Org. React.* 1997, *49*, 331.

Multistep Reactions

The [2+2+2] Cycloaddition

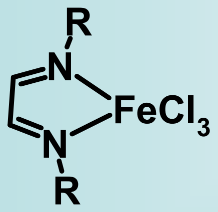
- important method of making six membered rings
- also, many of the other multistep processes are based on this reaction

-consider



-feasible reaction
-requires 400°; many side reactions
-not synthetically useful as such

-there are several transition metal fragments which allow this type of reaction to occur at much lower temperatures, including...

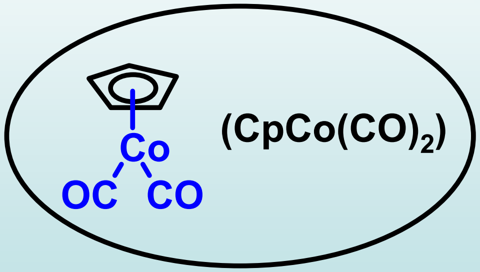


+ EtMgBr ;

$(Ph_3P)_3RhCl$;

Grigg, R.

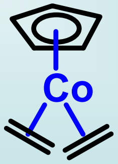
R Modern Rhodium Catalyzed Reactions Ch 7.3.1



$(CpCo(CO)_2)$

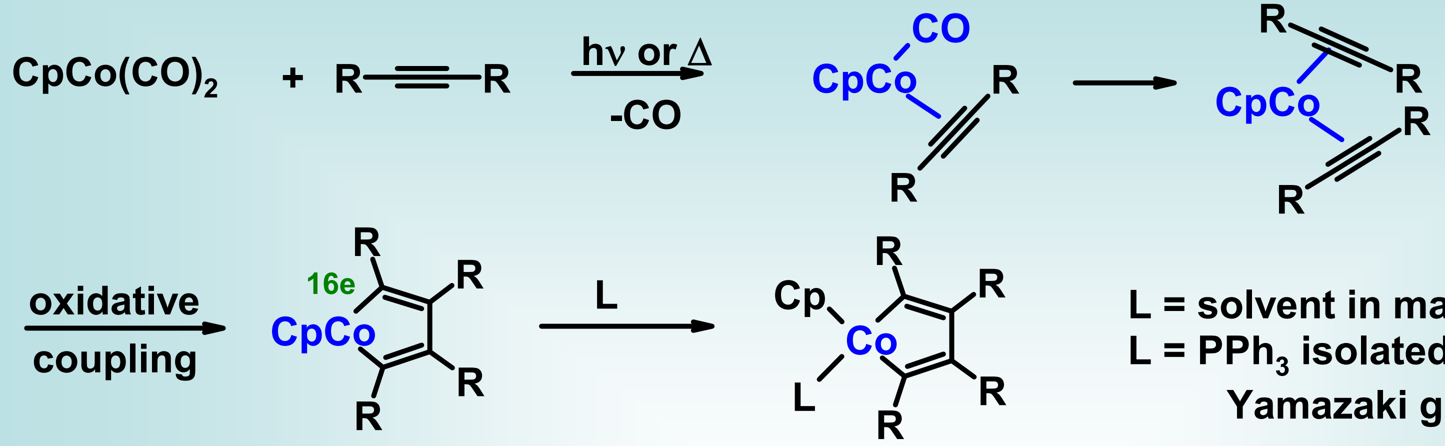
Vollhardt, K.P.C.

;



$(CpCo(ethene)_2)$

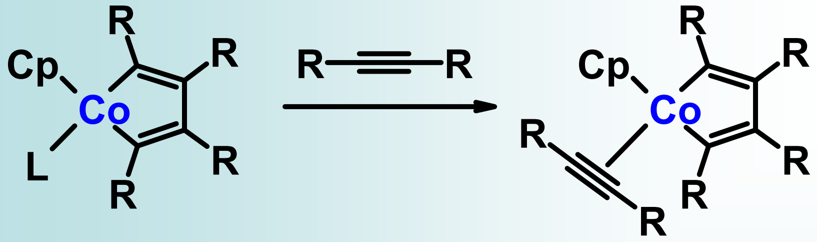
This reaction proceeds by a combination of fundamental steps we have seen before



L = solvent in many cases
L = PPh_3 isolated often by
Yamazaki group

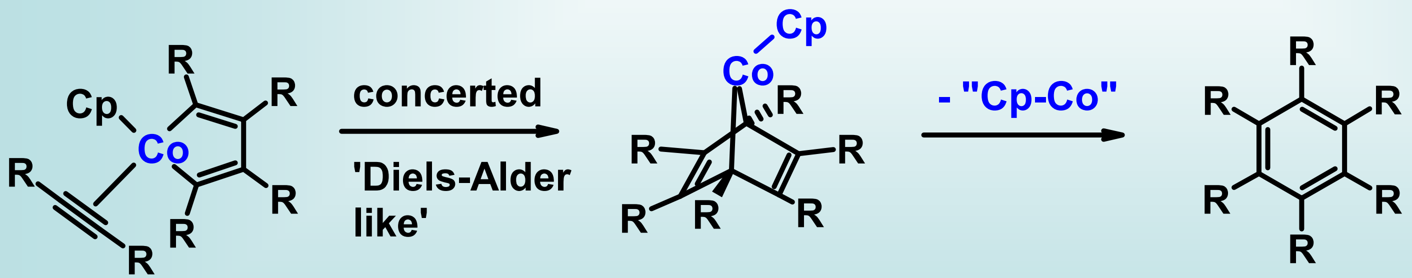
(*Tetrahedron Lett.* 1974, 4549; *J. Organomet. Chem.* 1977, *139*, 157;
J. Am. Chem. Soc. 1983, *105*, 1907.)

-then



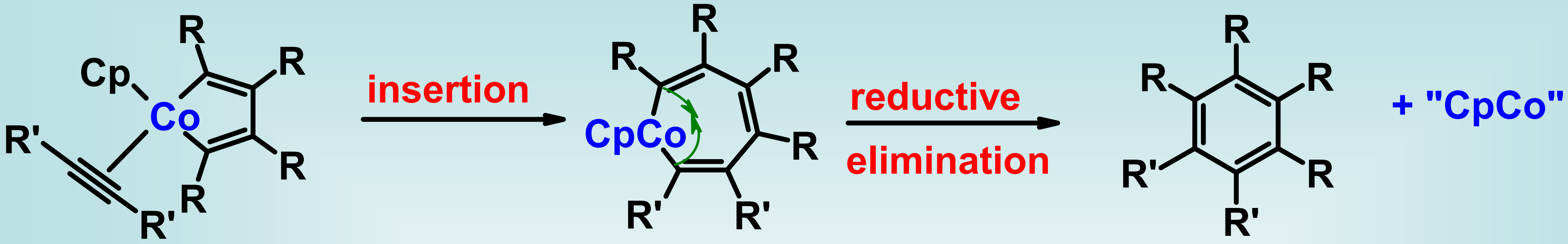
now comes uncertainty.......
-the next step is undecided between
two possibilities

Possibility #1 - concerted cycloaddition



"CpCo" regenerated; therefore possible to be catalytic in Co

Possibility #2 - Alkyne insertion/reductive elimination

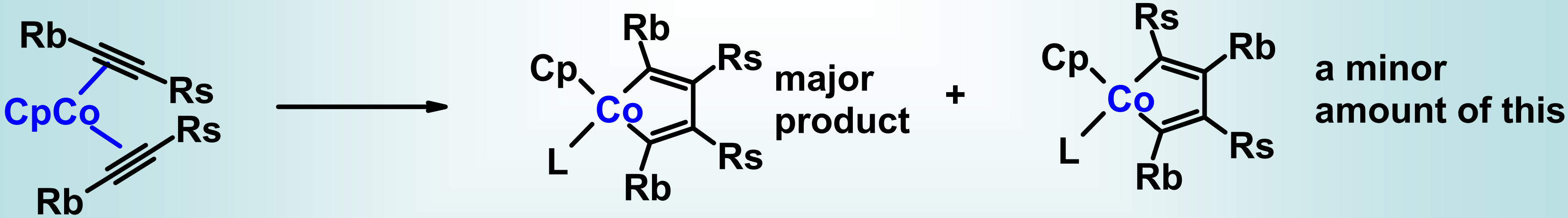


Personal opinion - there are instances where the concerted cycloaddition mechanism is operating

- <u>more often</u>, it is the insertion/elimination mechanism that is operating

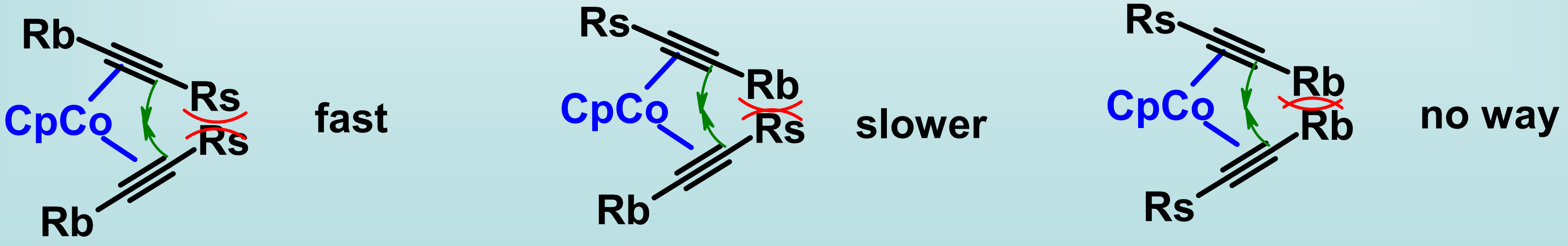
Regiochemistry

-if one has R(big)≡R(small) , what happens?



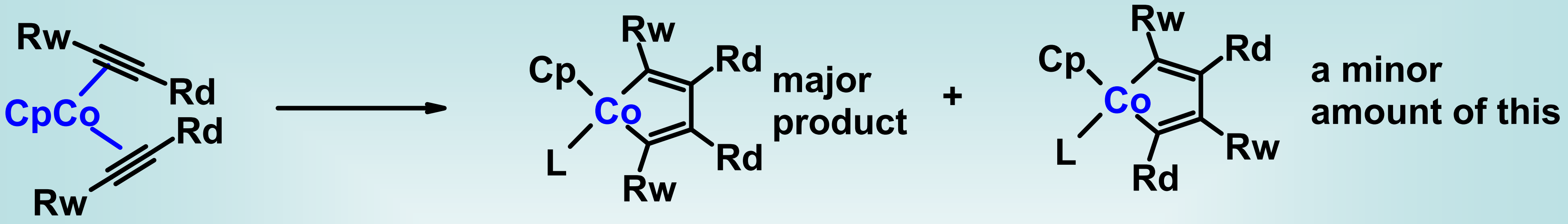
major product + a minor amount of this

-simply from sterics



fast slower no way

-if one has $R(EDG){\equiv}R(EWG)$, what happens?

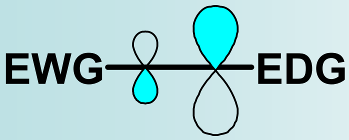


major product

a minor amount of this

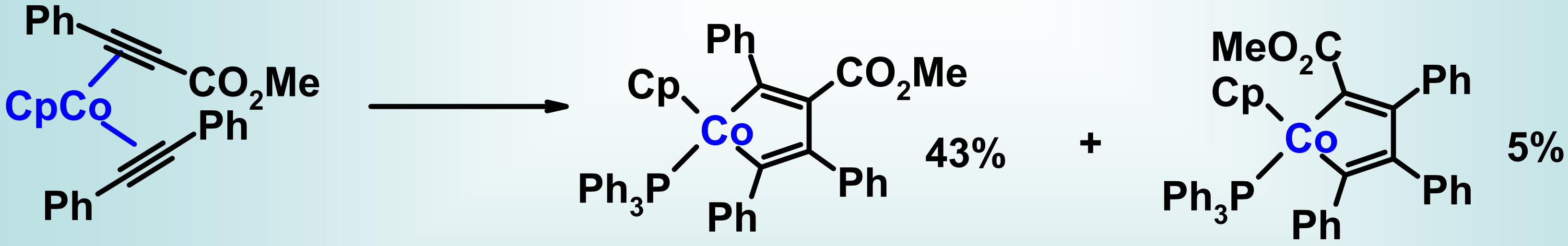
-reason - oxidative coupling step proposed to operate under orbital control

- HOMO of complex dominates, and <u>it</u> is domonated by the π* of the alkene



-therefore, C-C bond formation to give metallacycle occurs at the carbon β- to the EWG

-if sterics and electronic effects compete, the <u>steric</u> effect overwhelm



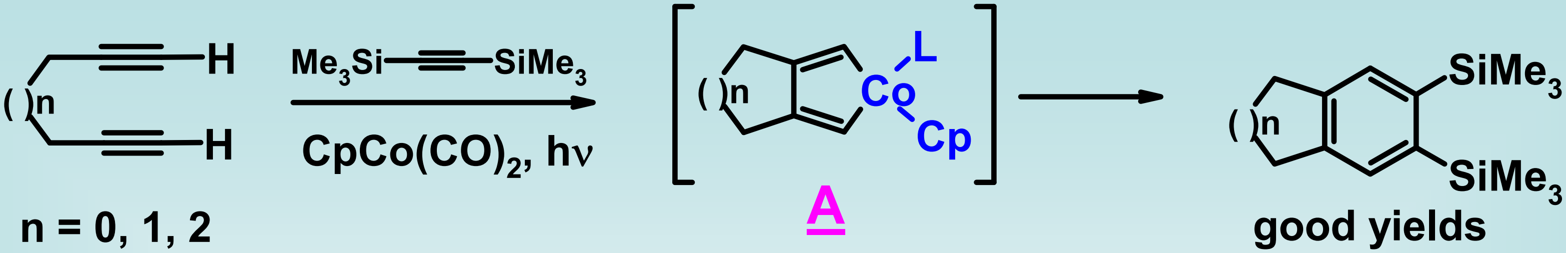
43%

5%

-there is still a third alkyne to participate in 2+2+2, so often one gets further regiochemical mixtures

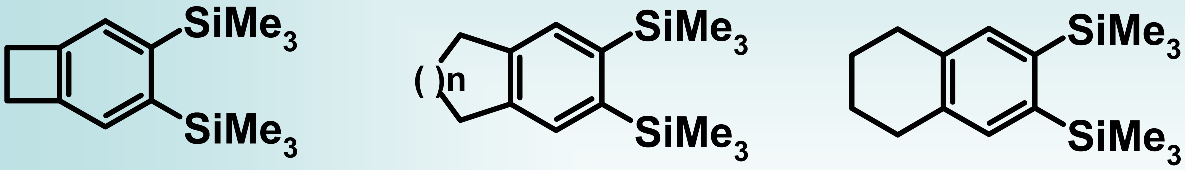
-reaction becomes synthetically useful when BTMSA $Me_3Si{\equiv}SiMe_3$ is used as the third alkyne, as it only reacts with itself very slowly

-particularly synthetically useful reaction when the two other alkynes are joined i.e.,

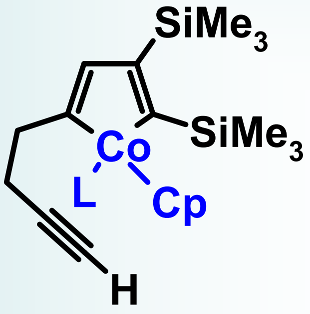


n = 0, 1, 2

good yields

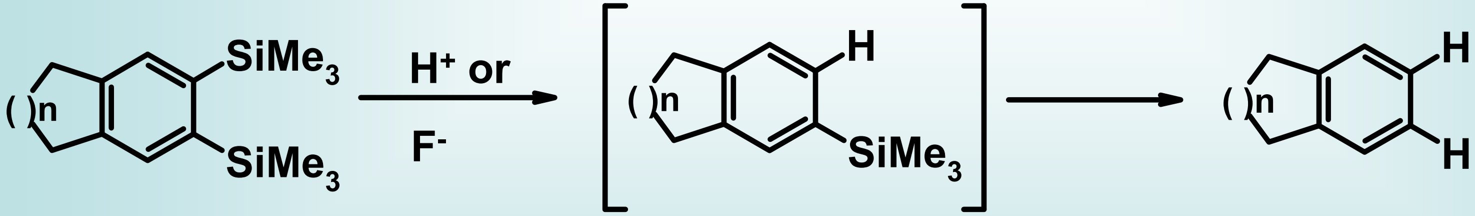


Note; in this case,
the rxn goes through



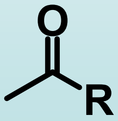
instead of <u>A</u>

-fortunately, silyl groups are removable from arenes

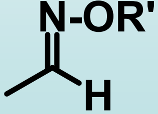


-reactions tolerate a pretty good range of substituents, such as... $-CO_2R$, $-CH_2OH$, $-CH_2OR'$,

$-NR'_2$, -SR',

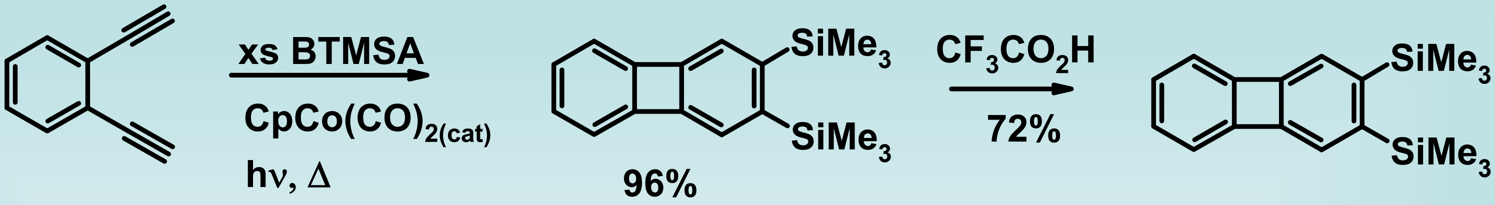

$CH_3C(=O)R$

,

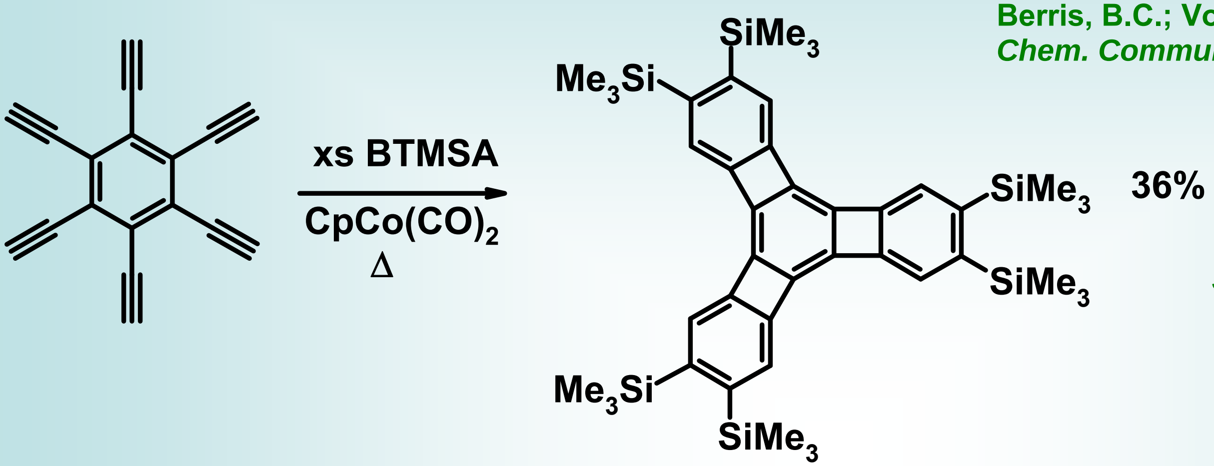

$CH_3CH=N{-}OR'$

-reaction may be carried out thermally or photochemically (or both)
-reaction is often (but not always) catalytic in cobalt

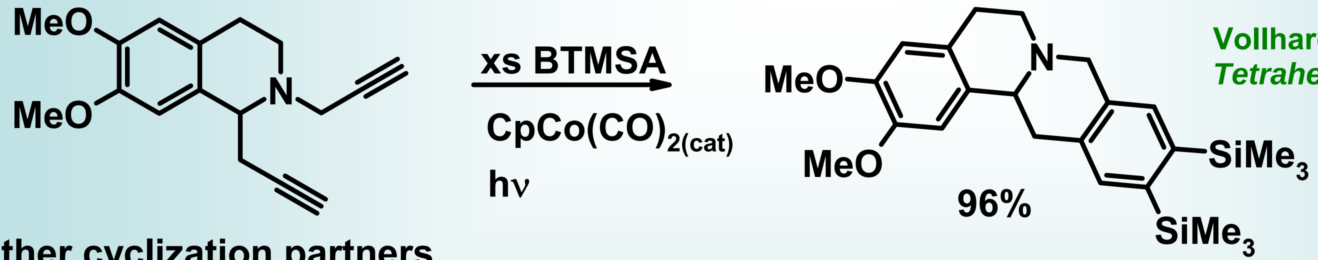
examples



Berris, B.C.; Vollhardt, K.P.C. *J. Chem. Soc., Chem. Commun.* 1982, 953.



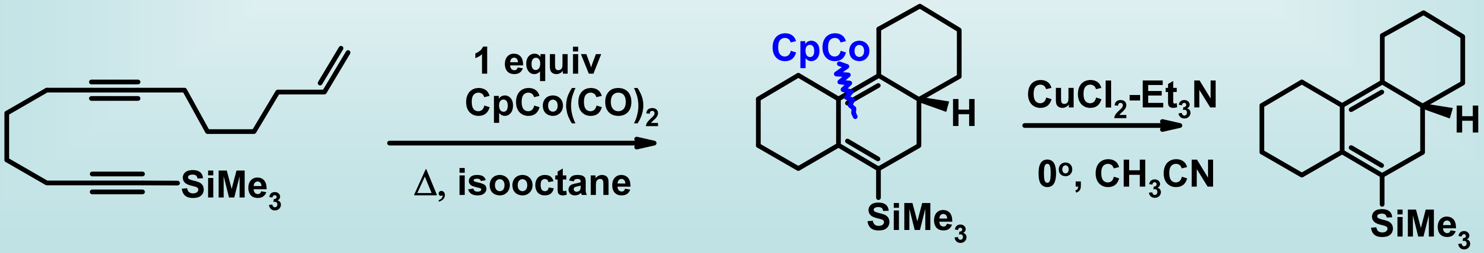
Dierks, R.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* 1983, *39*, 3150.



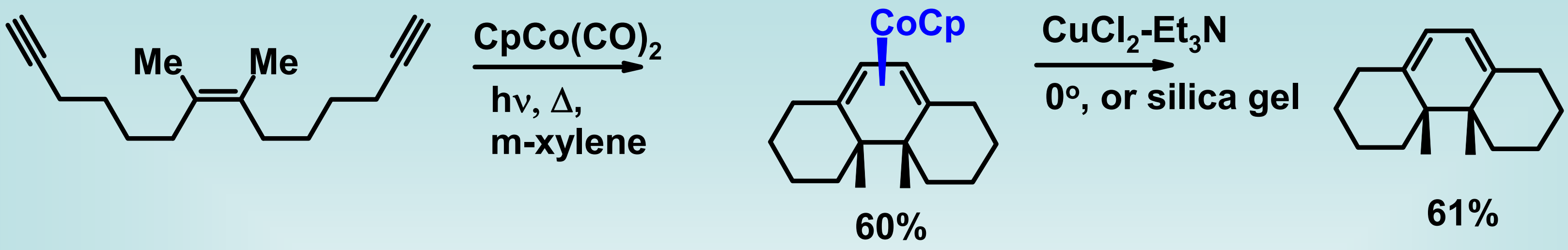
Vollhardt, K.P.C. et al *Tetrahedron* 1983, *39*, 905.

Other cyclization partners

-the 'third alkyne' does not have to be an alkyne *per se* - for example, it can be an alkyne



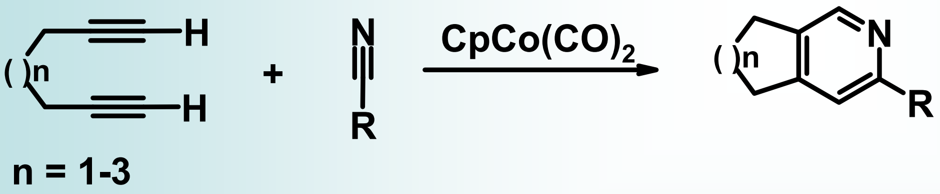
Sternberg, E.D.; Vollhardt, K.P.C. *J. Org. Chem.* 1984, *49*, 1564.



Vollahrdt, K.P.C. et al *J. Org. Chem.* 1984, *49*, 5010; *Angew. Chem. Int. Ed. Engl.* 1981, *20*, 802.

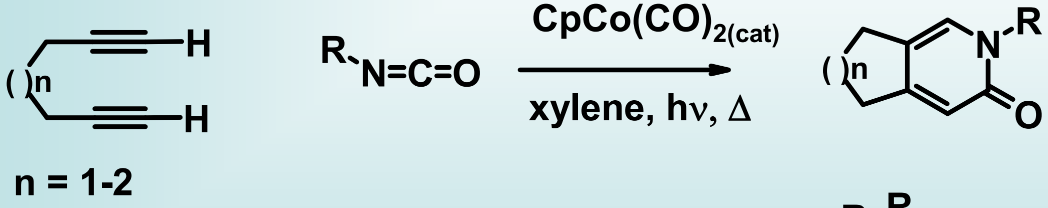
-in these cases, there must be at least one equivalent of Co
-must subsequently decomplex the Co-diene complex
-normally, the alkene is the 'third' partner

-the 'third' partner can also be a nitrile

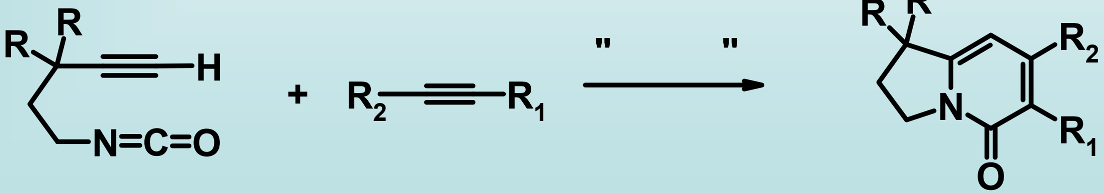


Vollhardt, K.P.C. et al *Tetrahedron* 1983, *39*, 905.

-or an isocyanate



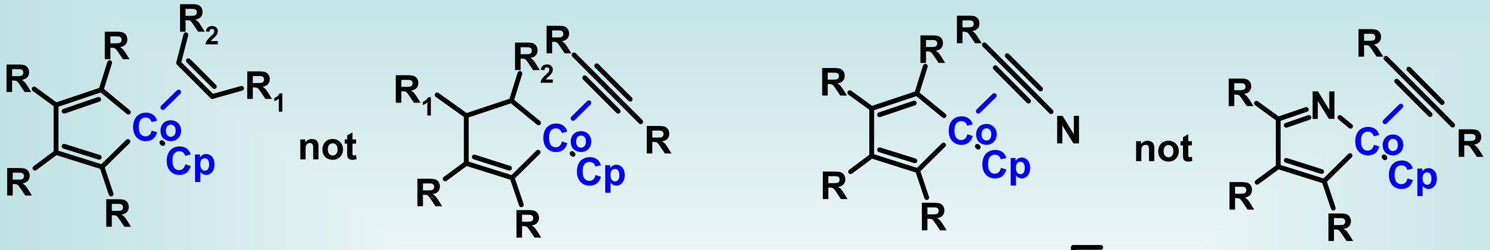
Earl, R.A.; Vollhardt, K.P.C.
J. Org. Chem. 1984, *49*, 4786.



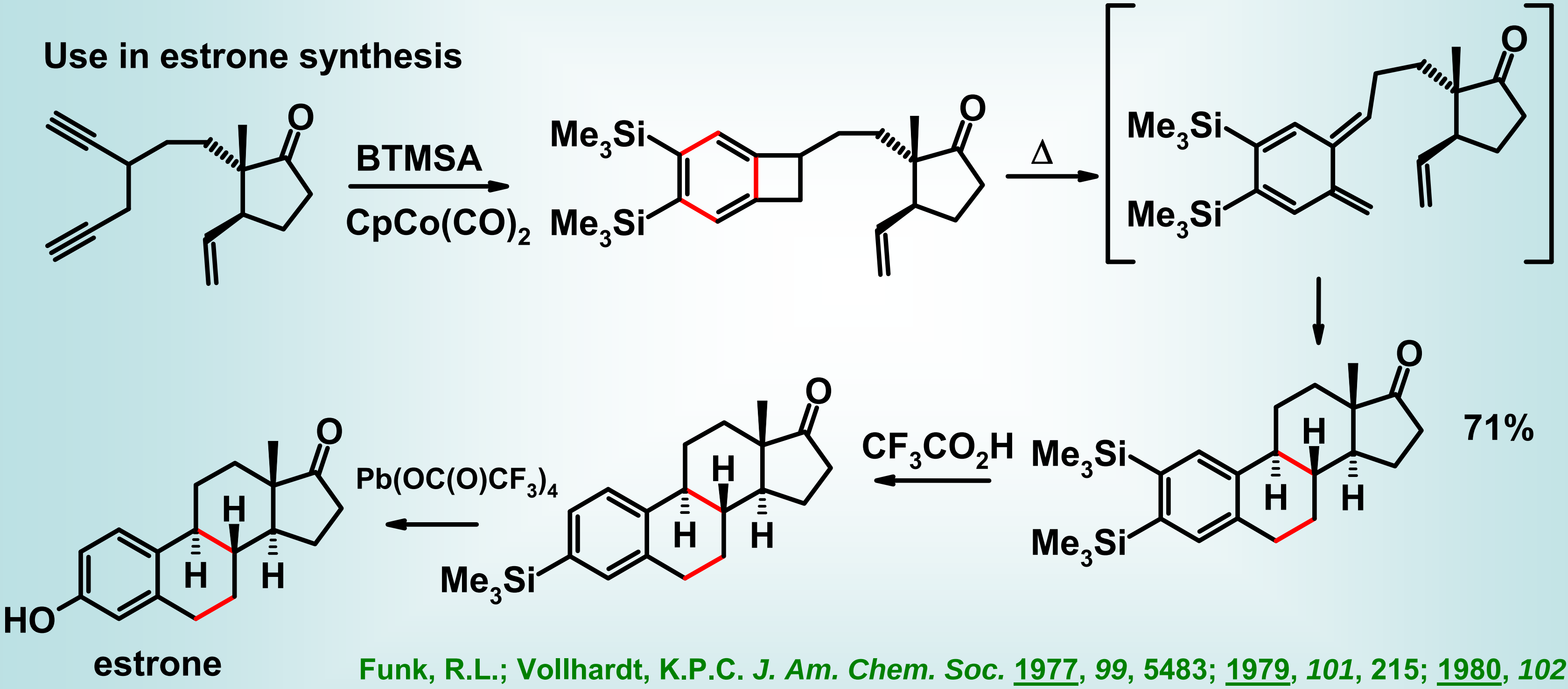
ca. 45%

-again, these are, in almost all circumstances, the 3rd partner in the cycloaddition

i.e.



Use in estrone synthesis

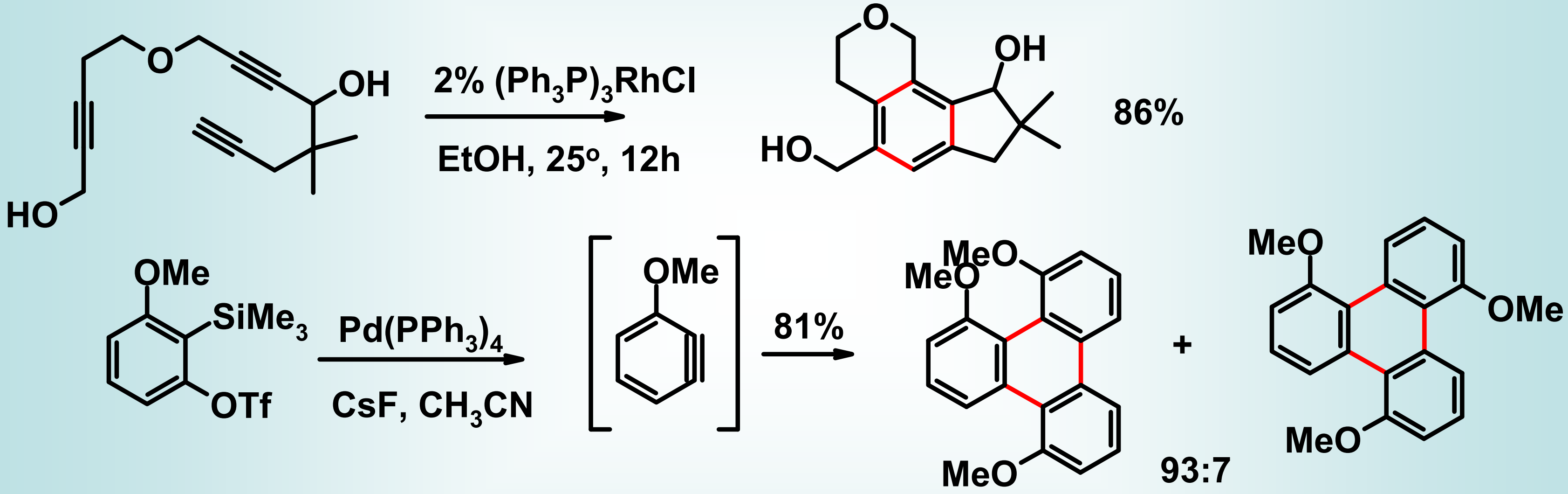


Funk, R.L.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* 1977, *99*, 5483; 1979, *101*, 215; 1980, *102*, 5253.

-using the Co^{I} / Co^{III} systems are not the only transition metal complexes capable of these cycloaddition - certainly the most popular, especially in early days, but other systems have been used effectively

-a survey of literature, early 2000's

$\mathrm{Rh^{I}/Rh^{III}}$	20	$\mathrm{Rh(PPh_3)_3Cl}$, $\mathrm{[RhCl(cod)_2]_2}$	$\mathrm{Ir^{I}/Ir^{III}}$	2
$\mathrm{Pd^{o}/Pd^{II}}$	15	$\mathrm{Pd(PPh_3)_4}$	$\mathrm{Ti^{II}/Ti^{IV}}$	2
$\mathrm{Ni^{o}/Ni^{II}}$	14	$\mathrm{Ni(cod)_2}$, (+ $\mathrm{PPh_3}$)	$\mathrm{Fe^{o}/Fe^{II}}$	1
$\mathrm{Co^{o}/Co^{II}}$	9	$\mathrm{Co_2(CO)_8}$	$\mathrm{Ta^{III}/Ta^{V}}$	1
$\mathrm{Ru^{II}/Ru^{IV}}$	5			
$\mathrm{Mo^{o}/Mo^{II}}$	3	$\mathrm{Mo(CO)_6}$		



Many, many reviews on this

R Tanaka, K. *Synlett* 2007, 1977. (Rh catalysts)

R Chopade, P.R.; Louie, J. *Adv. Synth. Catal.* 2006, *348*, 2307. (all metals)

R Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* 2006, 2209 (Co)

R Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* 2005, 4741 (all metals, small)

R Saito, S.; Yamamoto, Y. *Chem. Rev.* 2000, *100*, 2901 (all metals)

R Grotjahn, D.B. *Comprehensive Organometallic Chemistry II*, Vol12, p741, 1995 (library)

R Boese, R.; Sickle, A.P.; Vollhardt, K.P.C. *Synthesis* 1994, 1374. (indoles)

R Schore, N. *Comprehensive Organic Synthesis*, Vol 5, p 1129, 1991

R Vollhardt, K.P.C. *Angew. Chem. Int. Ed. Engl.* 1984, *23*, 539.

3. Interrupting the 2+2+2

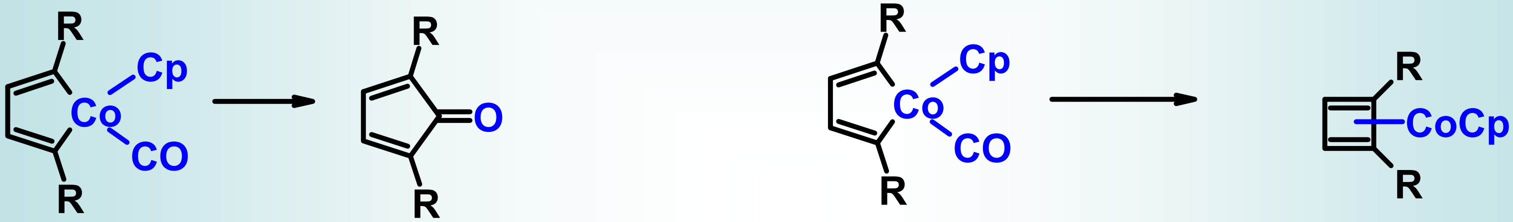
-there are a number of reactions that start to follow this 2+2+2 pathway, getting to the metallacyclopentdiene or metallacyclopentene, and then go differently

-only a time to look at a couple, but there are many more in synthesis

see: *Topics in Organometallic Chemistry* 2006, *19* entire issue

The Pauson-Khand Reaction

-two of the side products from the 2+2+2 are:

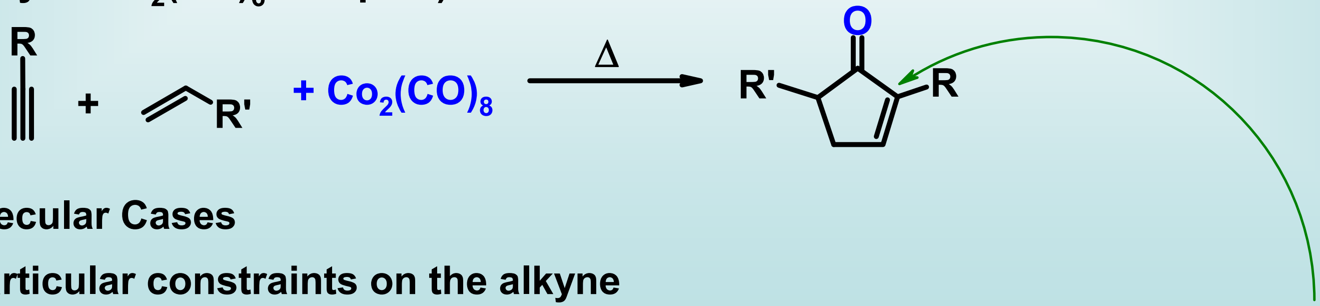


(Fe : Knolker, H.J.)

-cyclopentadienones are not very stable compounds, but if one of the C=C's is reduced, you have very useful cyclopentenones

-this type of material is often obtained by using and alkyne, and alkene, and $Co_2(CO)_6$ (or an alkyne-$Co_2(CO)_6$ complex)

i.e.,



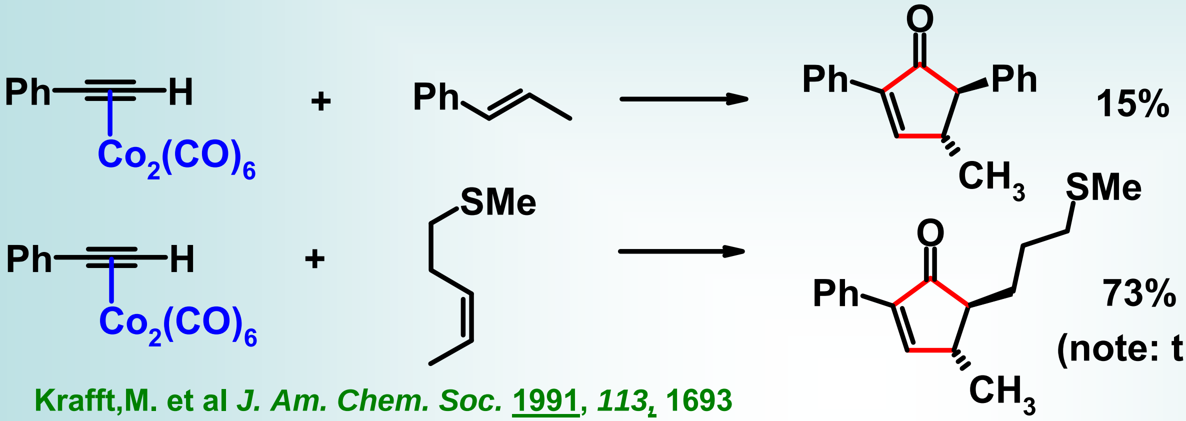
Intermolecular Cases

-no particular constraints on the alkyne

-if you have an unsymmetrical alkyne, larger groups end up next to C=O, as in

Alkene Partner

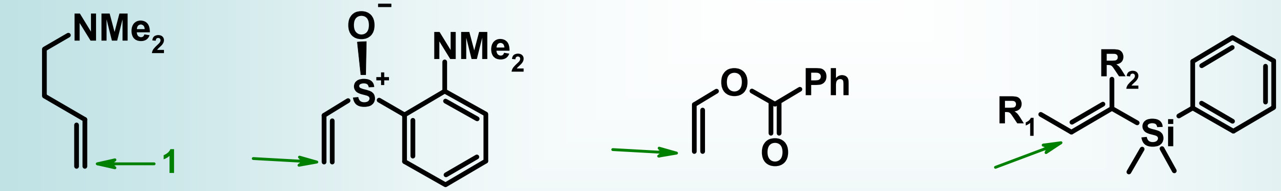
-simple alkenes don't work especially well, unless present in huge excess
(Note: this is making progress)
-strained alkenes, "non β-hydride" alkenes (bridged bicyclic akenes),
and alkenes with ligands attached (X = NR_2, SR, O?) give better yield, high regioselectivity



15% **ordinary alkene**

73% (note: trans) **coordinating substit.**

Krafft,M. et al *J. Am. Chem. Soc.* 1991, *113*, 1693



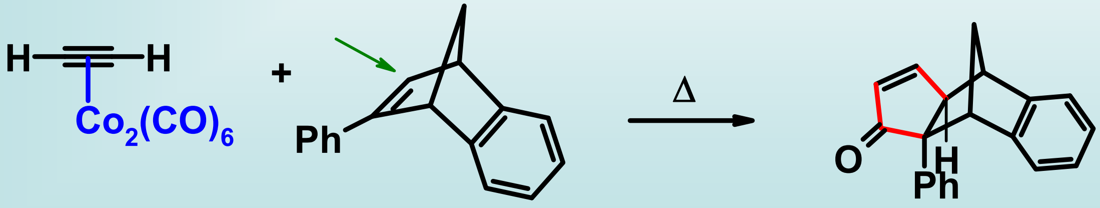
arrow is where 1st C-C bond forms

Krafft

Carretero
-also chiral

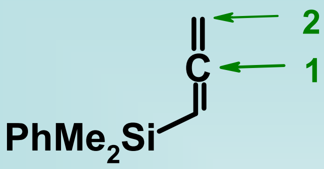
Kerr
-loses benzoate

Yoshida (with $Ru_3(CO)_{12}$)
-loses Si



bridged bicyclic alkene
(non β-hydride)

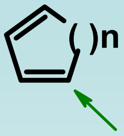
high %



Cazes (no β-H)

especially
n = small

even n = normal
with mild conditions



"no β-H"

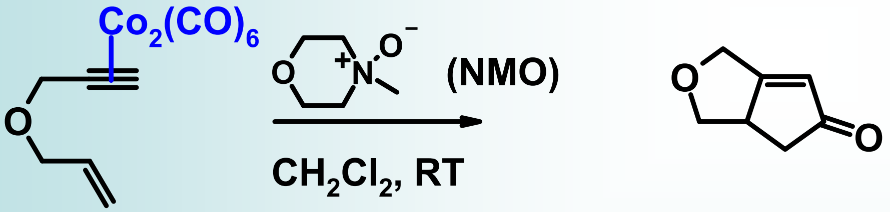
Reviews focussing on intermolecular reactions

R Gibson, S.E. et al *Angew. Chem. Int. Ed.* 2005, *44*, 3022.
R Laschat, S. *Synlett* 2005, 2547.

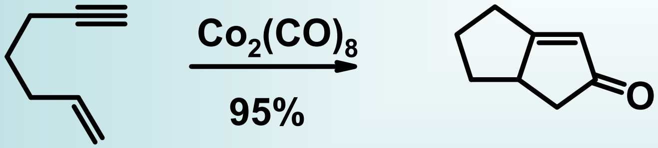
-except for sulphoxides, alkenes with EWG's rarely work

Intramolecular Cases

-reaction works much better when alkene and alkyne are in the same molecule

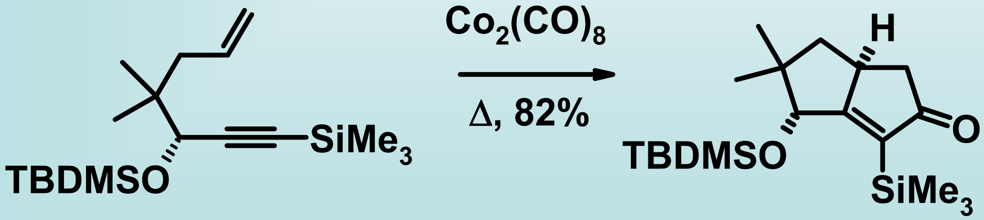


85%



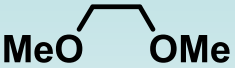
60% (old conds)

-often particularly good for all carbon bridges when there is a gem dialkyl in the bridge

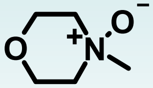


gem dimethyl or Thorpe-Ingold effect

-there are subtle stereochemical matters which are beyond this course's scope
-many recent advances have increased yields and allowed reactions under milder conditions

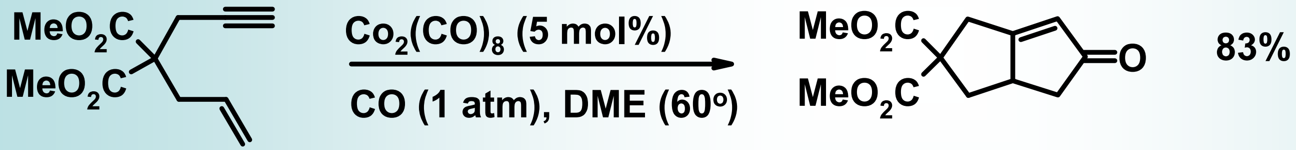
i.e., polar aprotic solvents (CH_3CN, DME )

-use of 1° amines ($CyNH_2$) and mercaptans (^nBuSMe) R Sugihara *Chem, Eur. J.* 2001, *7*, 1589

-photolysis
-3° amine oxides (Me_3N^+-O^-, TMANO), (NMO)  and room temp

Catalysis

-the new holy Grail - to use catalytic amounts of metal and CO gas (under as low a pressure as possible), or a CO substitute (some aldehydes)



-other metals (other than Co) now are common, especially for catalytic chemistry; I think that Rh^I is gradually replacing Co

Rh^I	25	$[RhCl(CO)_2]_2$
Mo^o	12	$Mo(CO)_6$ -allenes(Brummond)
Ru^o	8	$Ru_3(CO)_{12}$
Ir^I	4	
Ti^{II}	7	

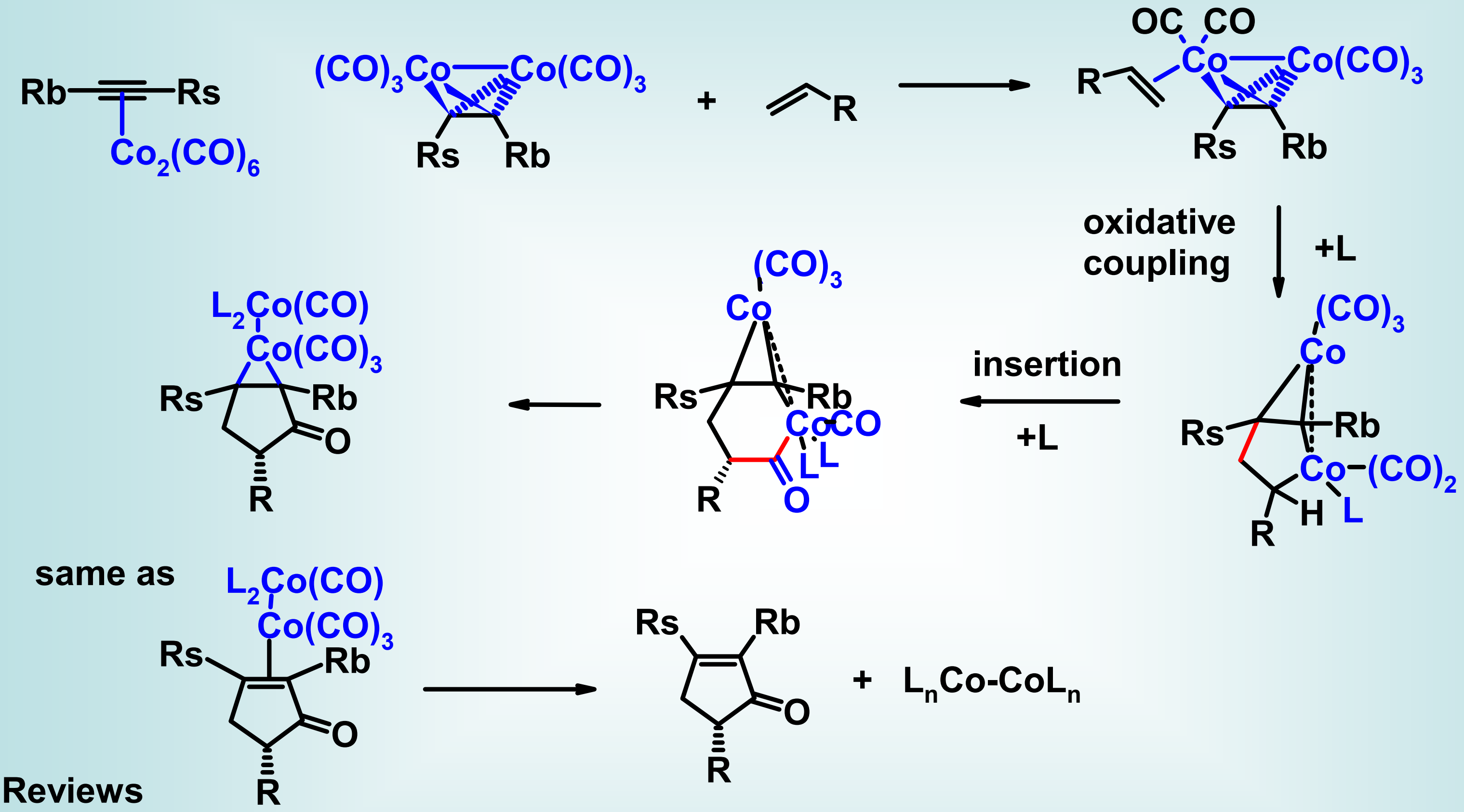
Zr^{II}	4
Fe^o, hν	4
Co nanoparticles	2
Co^I	1
W	1

Most recent reviews:

R Shibata,T. *Adv. Synth. Catal.* 2006, *348*, 2328.
R Pérez-Castells, J. *Top Organomet Chem* 2006, *19*, 207
R Strübing, D.; Beller, M. *Top Organomet Chem* 2006, *18*, 165

Mechanism of Pauson-Khand

-unnaturally complex looking, because presence of second metal, which is just 'along for the ride'

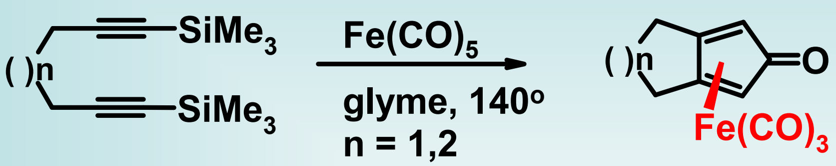


Reviews

- R Chung, Y.K. et al *Synlett* 2005, 545 (Co nanoparticles)
- R Krafft, M.E. *Tetrahedron* 2004, *66*, 9795. (Interrupted P.-K.)
- R Alcaide, J.C.; Almendros, P. *Eur. J. Org. Chem.* 2004, 3377 (allenes)
- R Perez-Castells, J. *Chem. Soc. Rev.* 2004, *33*, 32.
- R Gibson, S.E. *Angew. Chem. Int. Ed. Engl.* 2003, *42*, 1800 (catalytic)
- R Carretero, J.C. *Eur. J. Org. Chem.* 2002, *288*
- R Carretero, J.C. *Synlett* 2001, 26.
- R Brummond, K. *Tetrahedron* 2000, *56*, 3262 (allenes)
- R Geis, G.; Schmalz, H.-G. *Angew. Chem. Int. Ed. Engl.* 1998, *37*, 911
- R Schore, N.E. Comprehensive Organometal. Chem. II 1992, Vol 12, Ch 7.2
- R Schore, N.E. *Org. React.* 1991, *40*, 1.
- R Schore, N.E. *Chem. Rev.* 1988, *88*, 1081.

-so how about alkyne only cases, i.e.

-sort of - uses Fe° and product is the iron complex



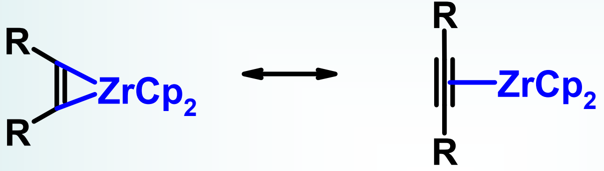
ca. 80%

R Knolker, H.-J. *Chem. Soc. Rev.* 1999, *28*, 151

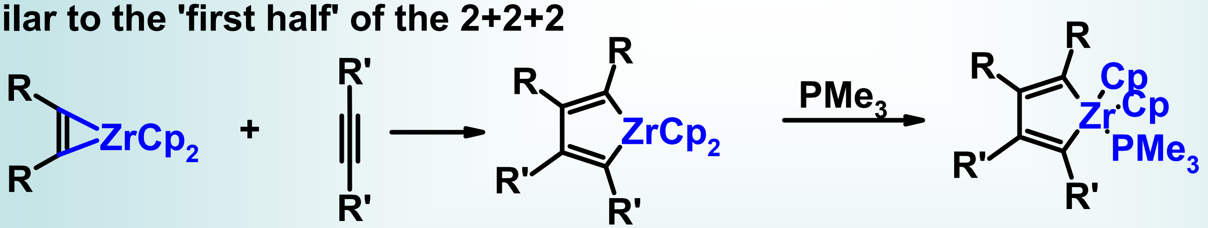
-decomplexation is not straight-forward, because cyclopentadienone is unstable (anti-aromatic)

The [2+2+????] Reactions of Zirconium Alkyne Complexes

-compounds like



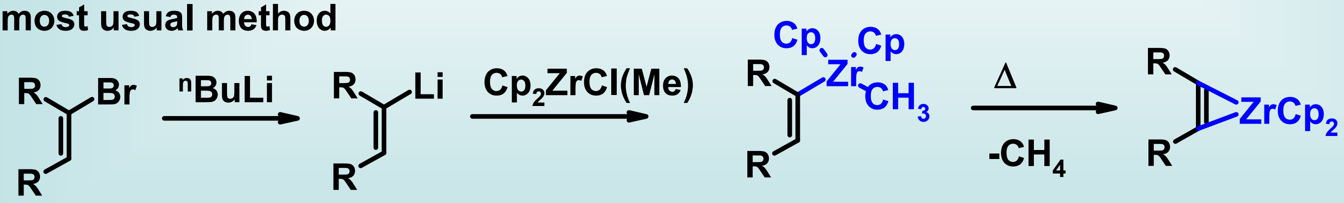
-also react with alkynes, alkenes, nitriles, to form C-C bonds by oxidative coupling process, similar to the 'first half' of the 2+2+2



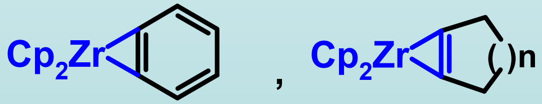
-can be isolated as the PMe_3 adduct

-the zirconocene alkyne complexes themselves are made differently than in Co case

-most usual method



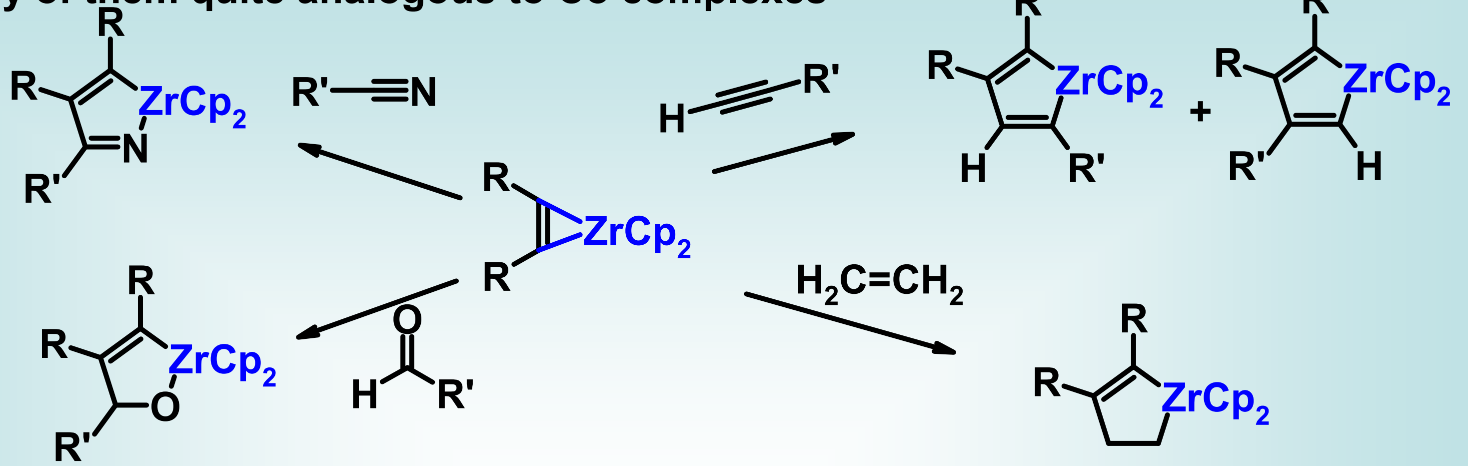
R cannot be H,



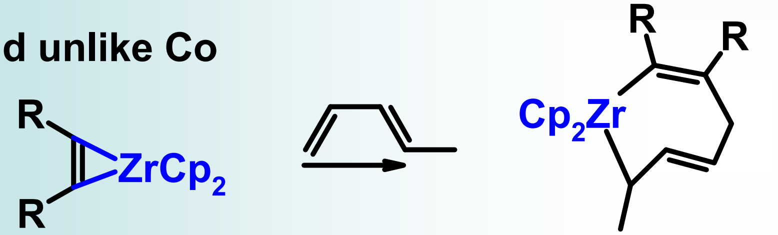
also made this way

Reactions Encountered

-many of them quite analogous to Co complexes

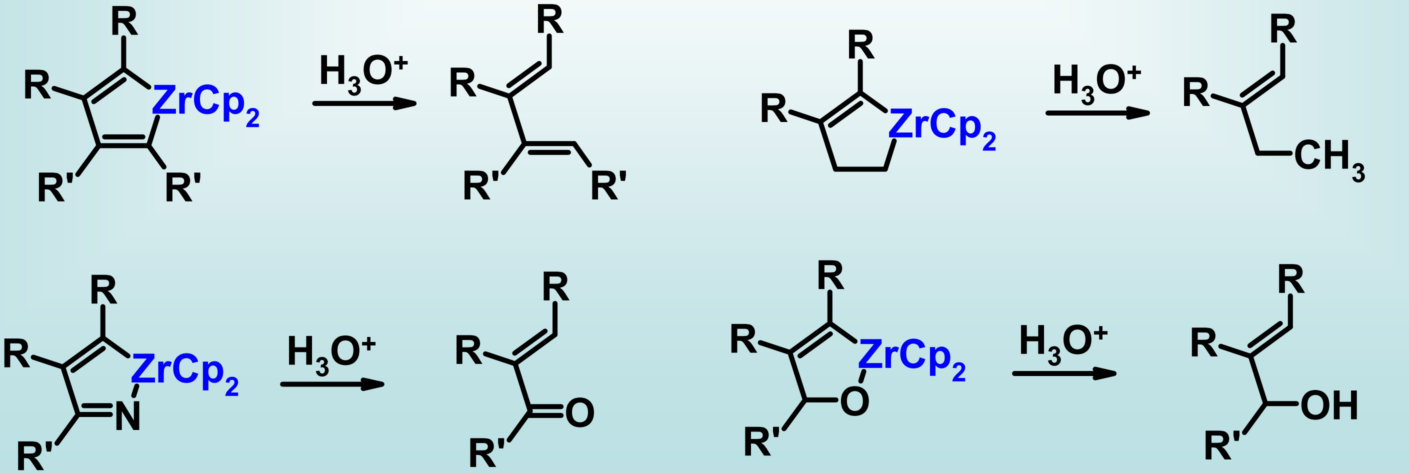


and unlike Co

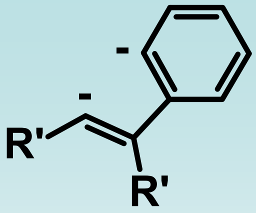


-are further reaction possible? - YES

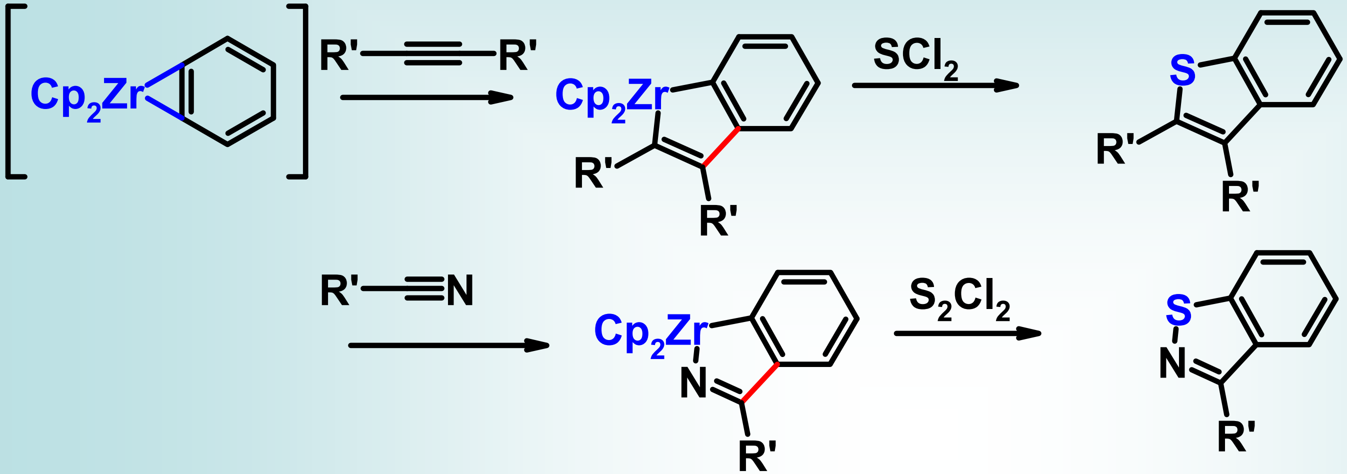
-most common is hydrolysis



-due to electronegativity difference between C and Zr, there's a tendency for these to react like



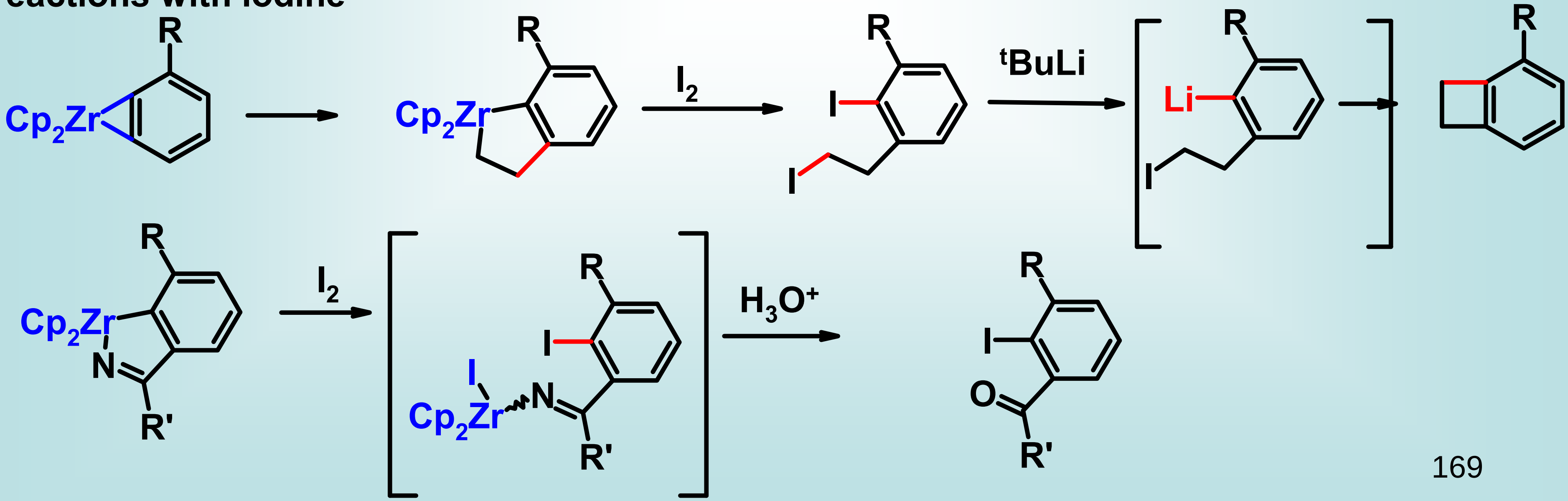
-other reactions -with sulphur monochloride or dichloride



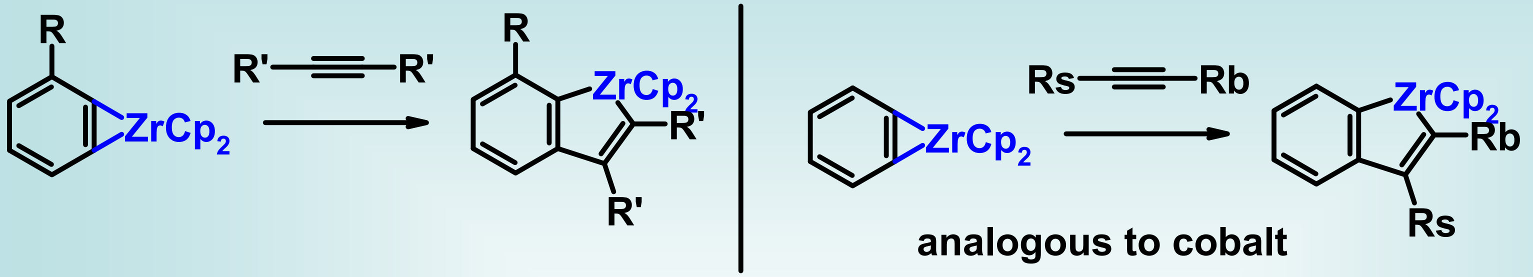
benzothiophenes

benzothiazoles

-reactions with iodine

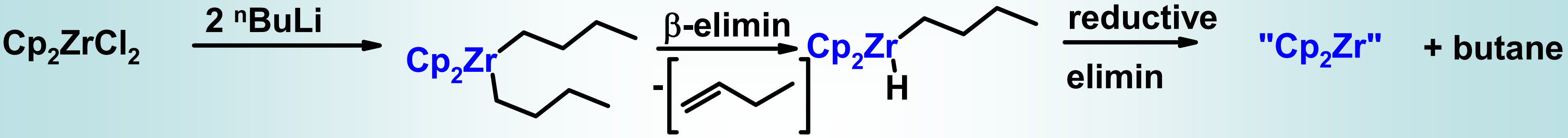


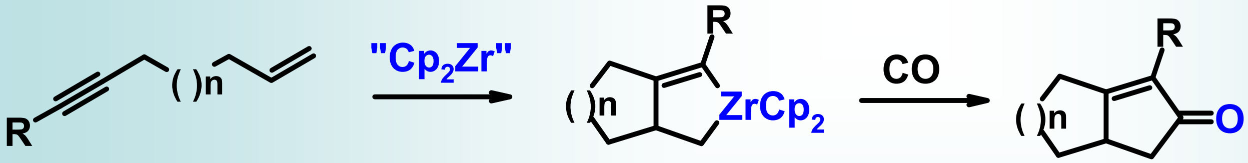
Regiochemistry in benzyne reactivity



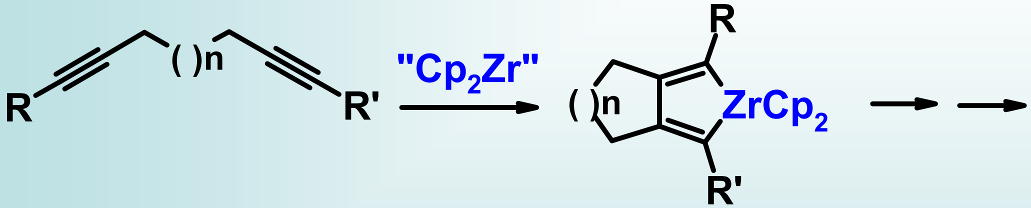
analogous to cobalt

Intramolecular cases - E.I. Negishi





Pauson-Khand



same reactions as
intermolecular cases

see

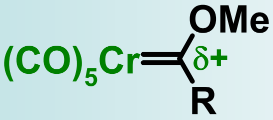
R Negishi, E.; Takahashi, T. *Bull. Chem. Soc. of Jpn.* 1998, *71*, 755.
R Majoral, J.-P. et al *Coord. Chem. Rev.* 1998, *178-80*, 145 (main group elements)
R Negishi, E. *Acc. Chem. Res.* 1994, *27*, 124.
R Buchwald, S.L.; Nielsen, R.B. *Science* 1993, *261*, 1696.
R Buchwald, S.L. *Chem. Rev.* 1988, *88*, 1047.

Carbenes

$L_nM{=}CH_2$ (carbenes or alkylidenes)

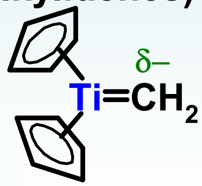
-structurally discrete carnes 'officially' fall into two types, characterized by their reactivity
 -I will arbitrarily add a third class

Fischer Type Carbenes



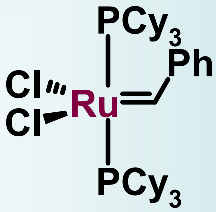
-mostly Cr group (Cr, Mo, W),
 or Fe group
-stabilized by heteroatom (O here)
-reactivity - electron poor at C

Schrock Type Carbenes (alkylidenes)



-early transition metal
-electron rich at carbon

Methesis Carbenes



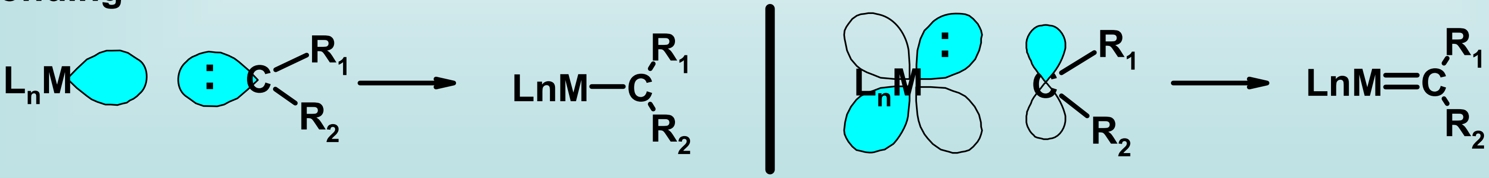
- early development by Schrock, so often lumped in with Schrock carbenes for convenience

-mid- or late transition metals
-no great M-C bond polarity,
 so C electronically neutral
-mostly cycloaddition processes

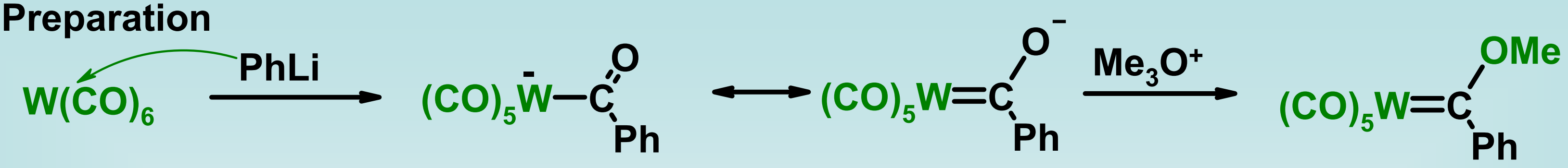
Fischer Carbenes

R de Meijere, A. et al *Angew. Chem. Int. Ed. Engl.* 2000, *39*, 3964
R Barluenga, J. *J. Organomet. Chem.* 2005, *690*, 539.

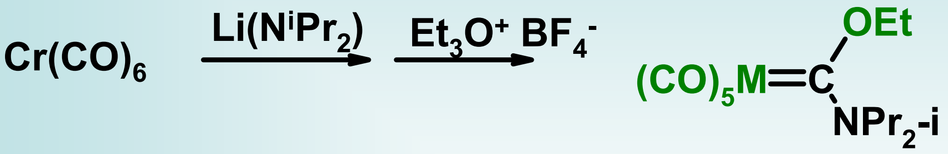
Bonding



Preparation

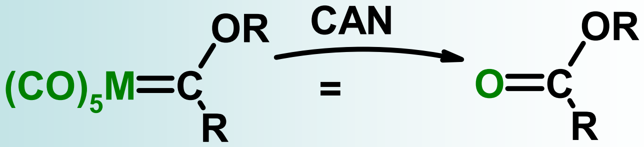


-nucleophiles mostly alkyllithiums, but don't absolutely have to be C based



Reactions of Fischer Carbenes

-for many reactions, it's useful to think of these carbenes as having parallel reactivity to carboxylic esters



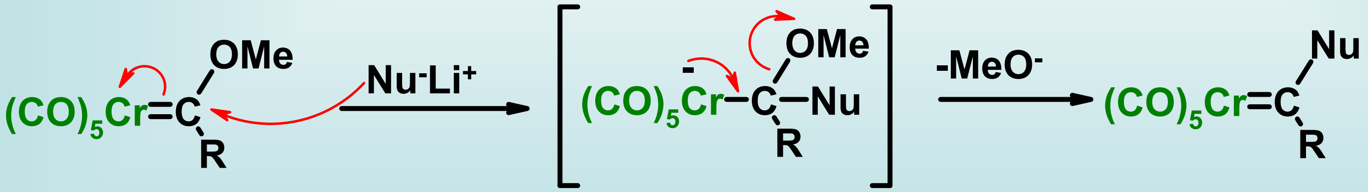
-can actually do the transformation with Ce^{IV}

a) Nucleophilic Attack at Carbene Carbon

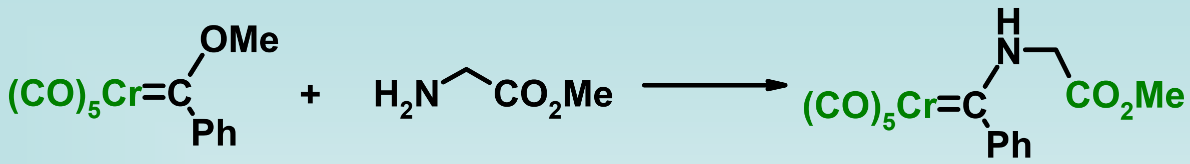
-calculations show that the LUMO of these species is localized at the carbene carbon

(Blick, T.F.; Fenske, R.F.; Casey, C.P. *J. Am. Chem. Soc.* 1976, *98*, 143)

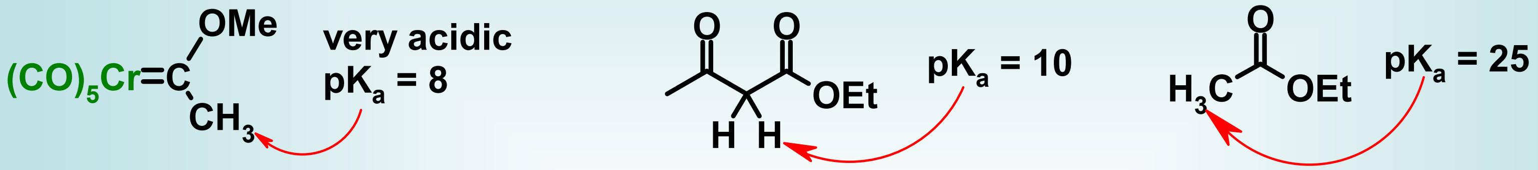
-attack of nucleophile, orbital controlled, is at that site

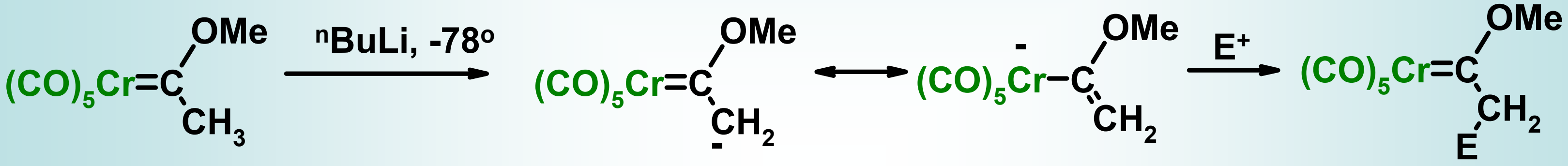


nucleophiles include	organolithiums RLi	amines R'$_2$NH	mercaptans RSH

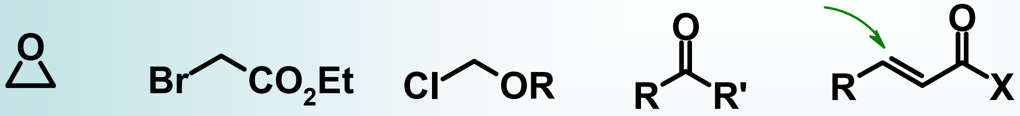


b) Generation of α-Anion and Electrophile capture



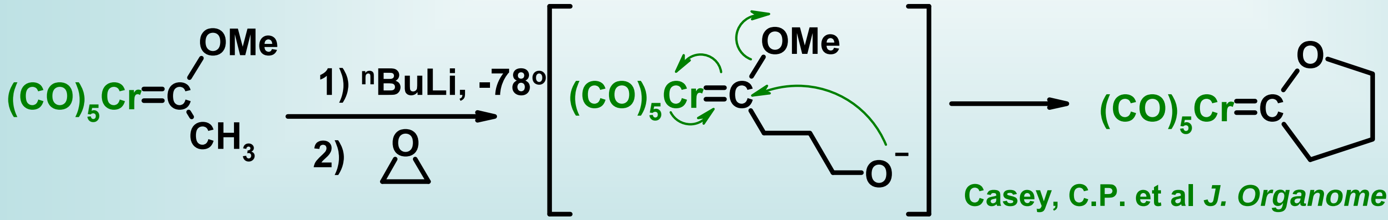


-anion is so stabilized that it's a fairly weak nucleophile; therefore only captures more reactive electrophiles



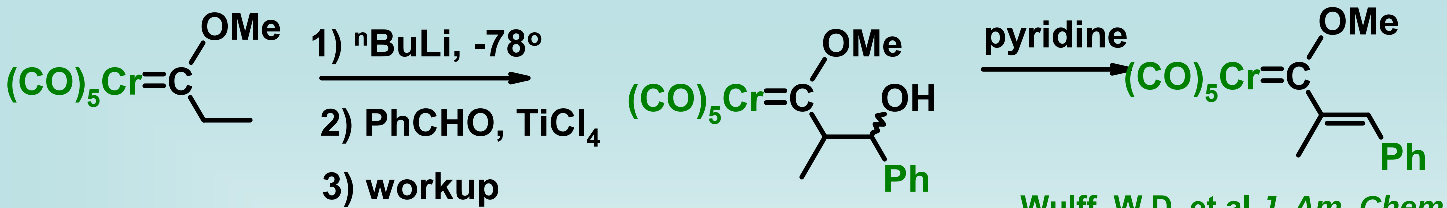
(Michael acceptor)

-epoxides give further reaction



Casey, C.P. et al *J. Organomet. Chem.* 1974, *73*, C28.

-aldehydes and ketones don't eliminate immediately, but the alcohols can be made to eliminate



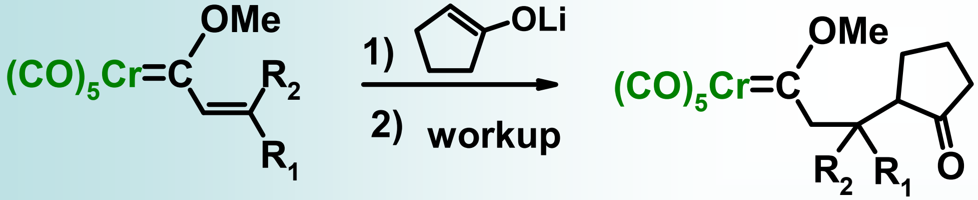
Wulff, W.D. et al *J. Am. Chem. Soc.* 1985, *107*, 503.

-can make the anion less stable, more reactive, by exchanging one CO ligand for a phosphine; the anion will then react with (less electrophilic) alkyl halides/triflates

Wulff, W.D. et al *J. Org. Chem.* 1987, *52, 3263*.

Michael Addition to Vinyl Carbenes

-since the α-anions are so stabilized, it's not suprising that reactions that give such an anion go well.......



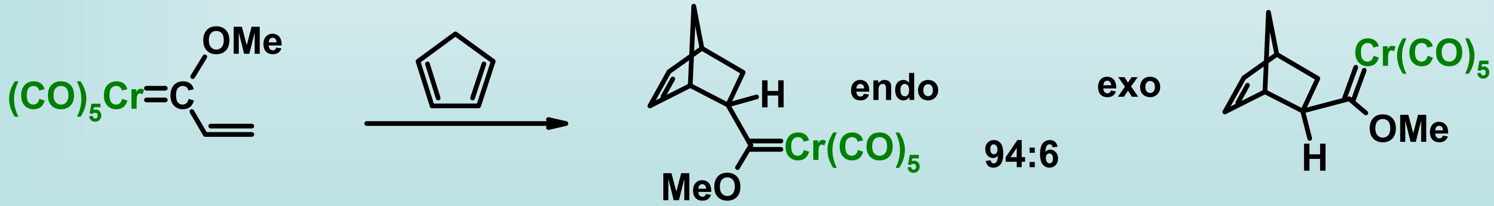
Nakamura, E. *J. Am. Chem. Soc.* 1993, *115*, 9015.

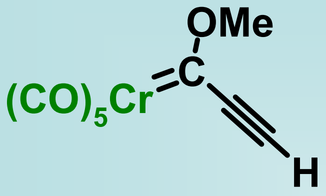
-can be highly stereoselective

Note: some anions add to carbene carbon, to give other products

Diels Alder Reaction of Vinyl Carbenes

- due to the strongly EWG nature of carbene, vinyl carbenes are more reactive (10^4 x) more reactive as dienophiles in 4+2 cycloadditions



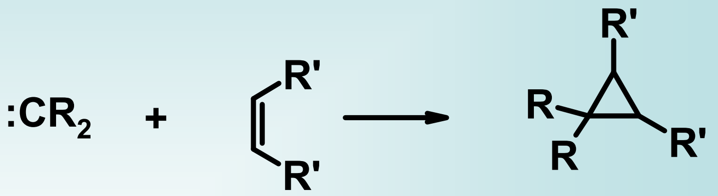


also
partcicpate

Wulff, W.D. et al *J. Am. Chem. Soc.* 1983, *105*, 6726
Dotz, K.H. et al *Angew. Chem. int. Ed. Engl.* 1986, *25*, 812
Wulff, W.D. et al *J. Am. Chem. Soc.* 1984, *106*, 756.

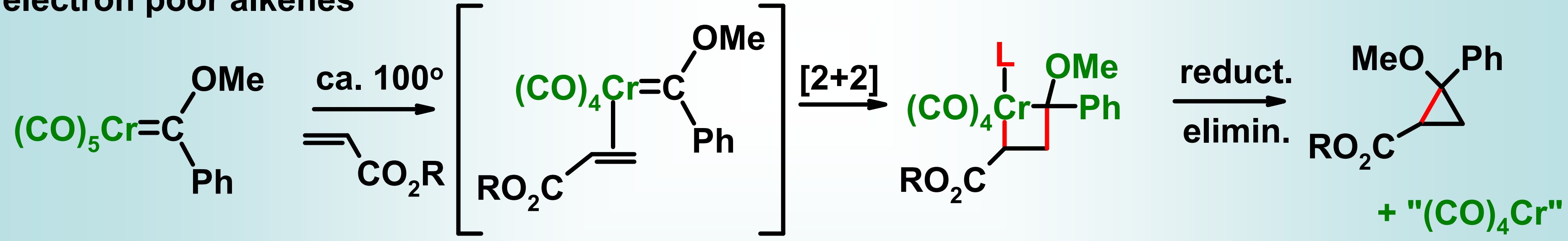
Cyclopropanation with Alkenes

-typical reaction of carbenes in organic chemistry

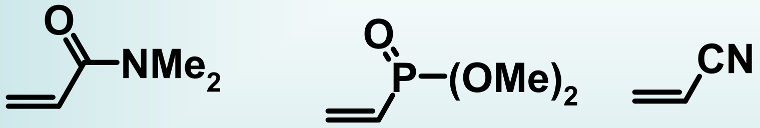


-may also be done with discrete organometallic complexes, with either electron poor or electron rich alkenes - probably by two different mechanisms

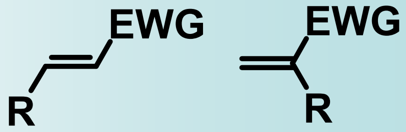
electron poor alkenes



-works with

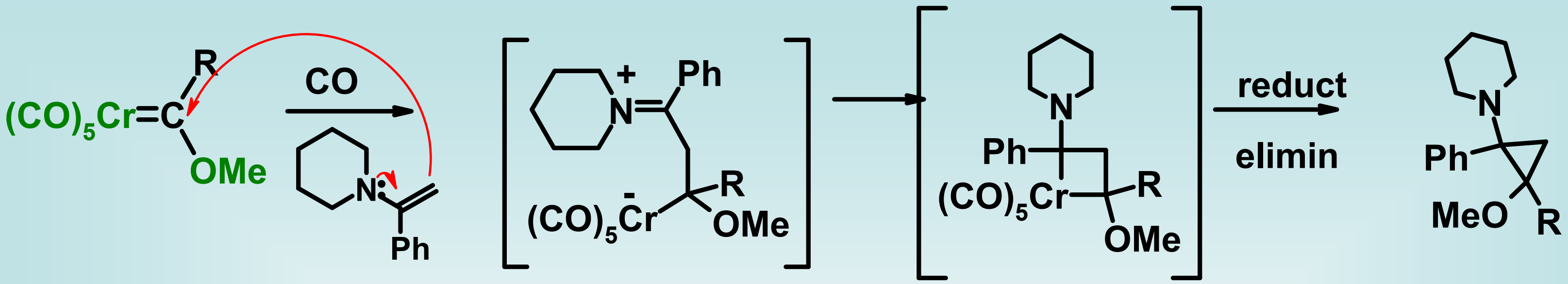


and disubstituted cases, i.e.,

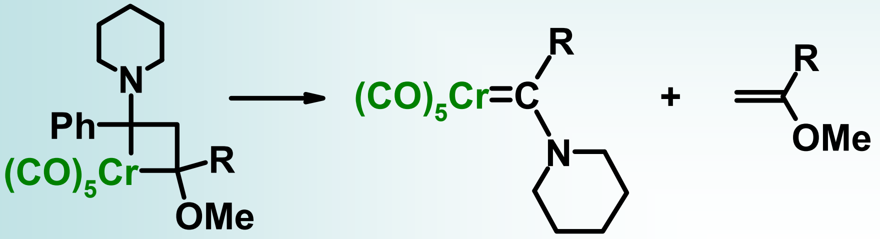


R Reibig, H.-U. "Organometallics in Organic Synthesis", V2, 1987, p.31
R Dotz, K.H. *Angew. Chem. Int. ed. Engl.* 1984, *23*, 587.
R Wu, Y,-T., Kurahashi, T., De Meijere, A. *J. Organomet. Chem.* 2005, *690*, 5900.
R Barluenga, J.; Rodríguez, F.; Fañanás, F.J.; Flórez, J. *Top. Organomet. Chem.* 2004, *13*, 59.

-with electron rich alkenes, rxns are at lower temperature, different mechanism

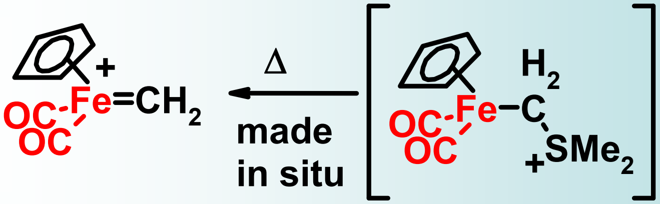


-reaction done under CO atmosphere to suppress alkene metathesis



-with normal alkenes, it's more useful to use

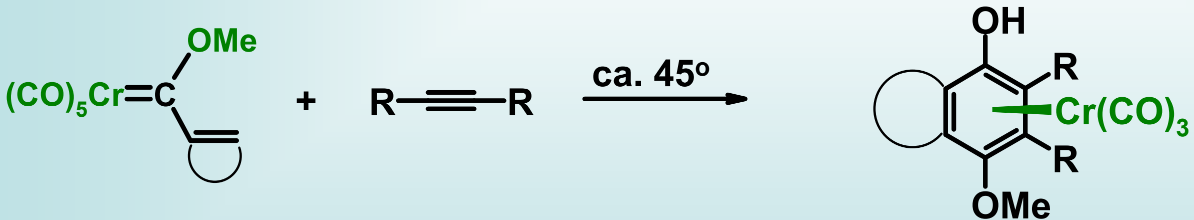
-see R Helquist, P. *Adv. Met. Org. Chem.* 1991, *2*, 143



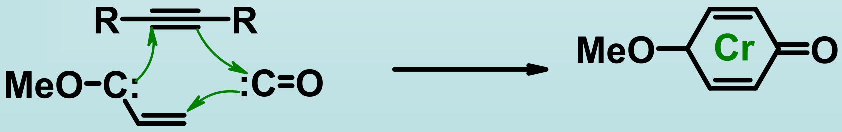
Carbene-Alkyne Cycloaddition

-probably most important type of rxn of Fischer carbenes; many uses in organic synthesis

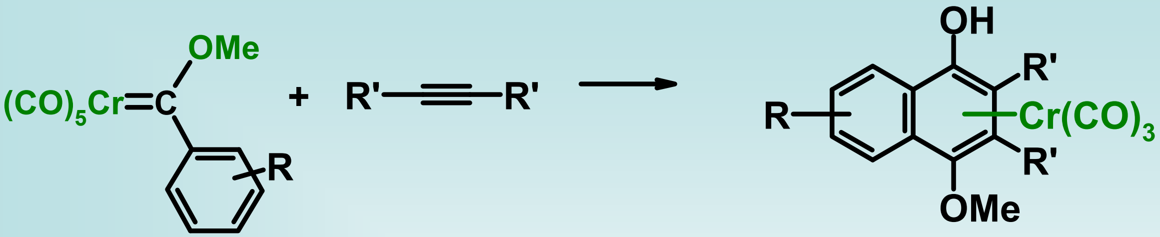
-vinyl and aryl carbenes do a 2+2+1+1 cycloaddition reaction to give very specific types of arenes



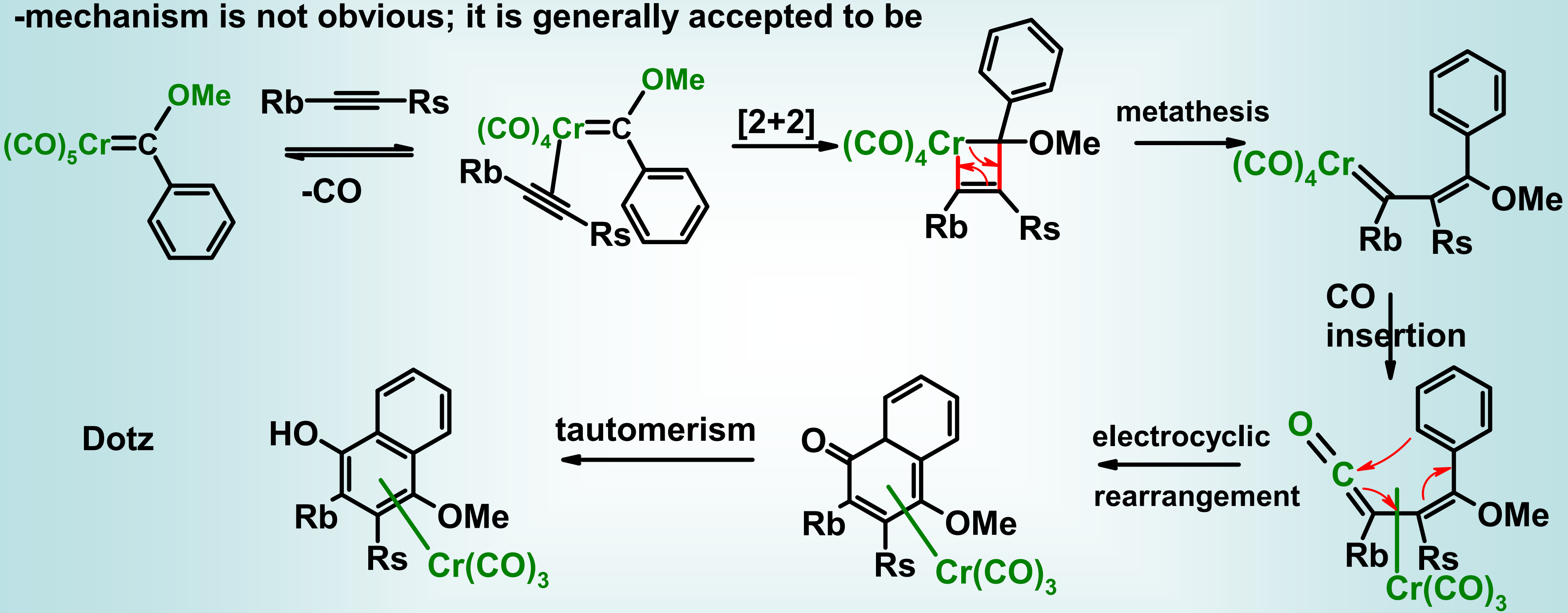
reaction is essentially



-this process also occurs on aryl substituted carbenes

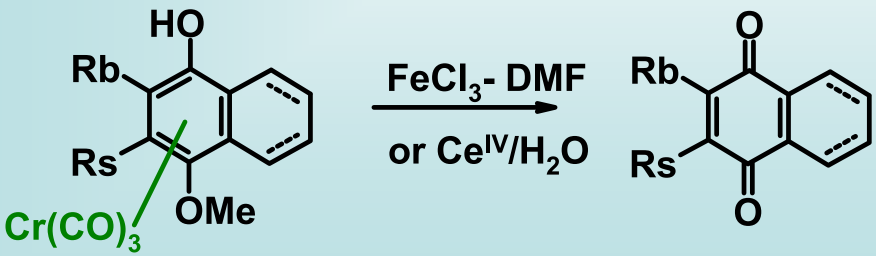


-mechanism is not obvious; it is generally accepted to be

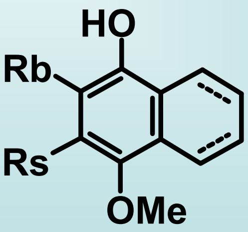


Dotz

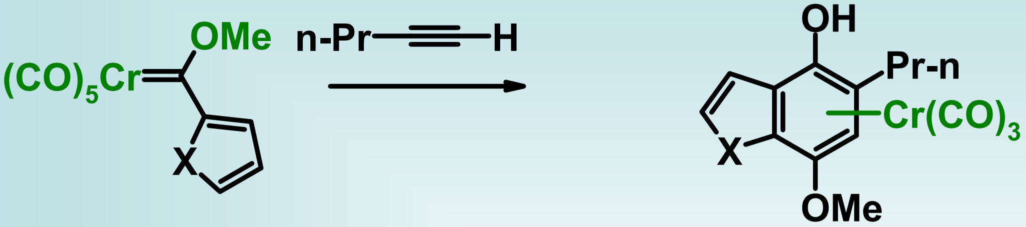
-easy to decomplex Chromium from arene



sometimes get

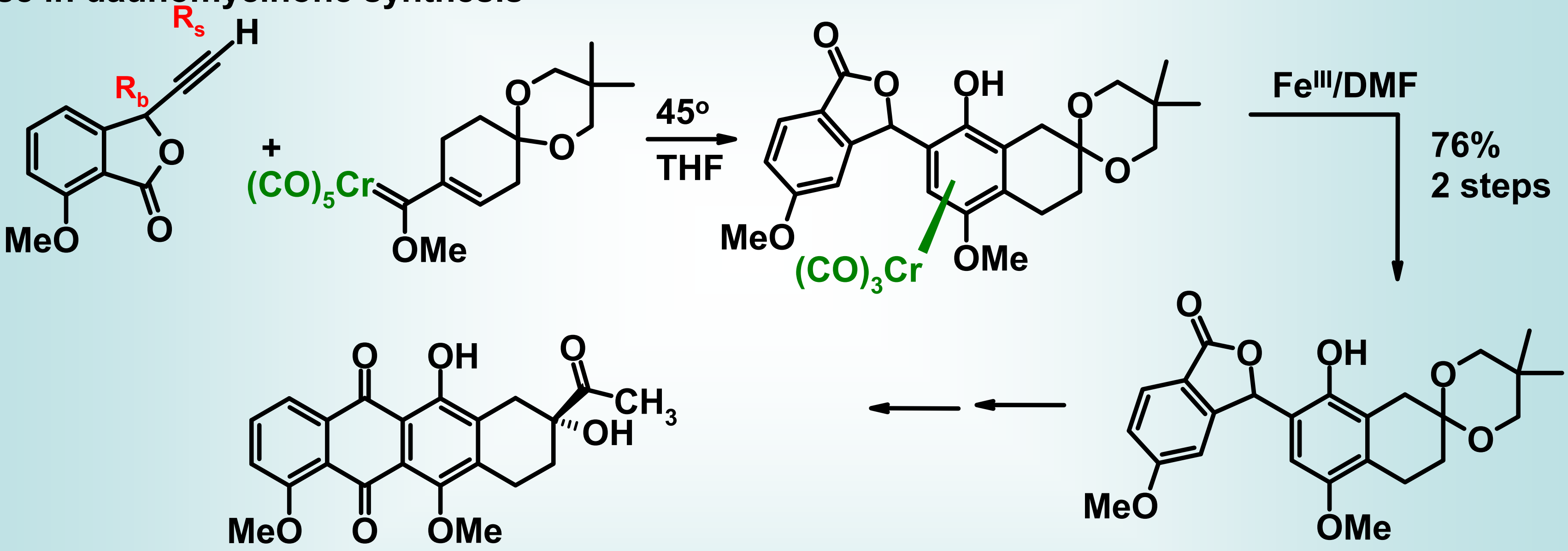


-aromatic heterocycles participate as well



X = O, S

-use in daunomycinone synthesis

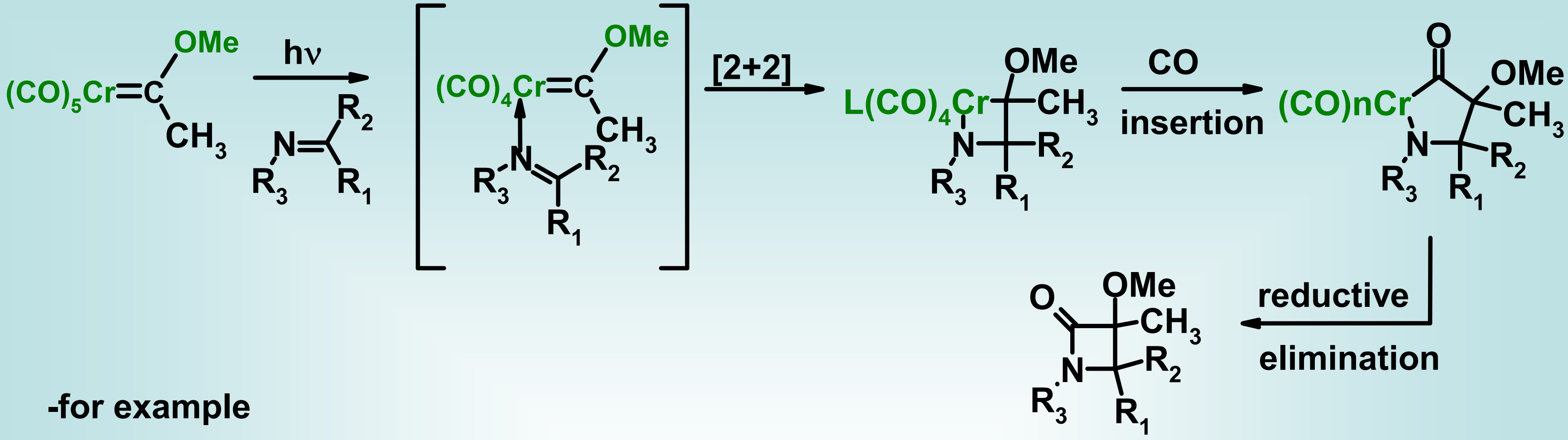


daunomycinone

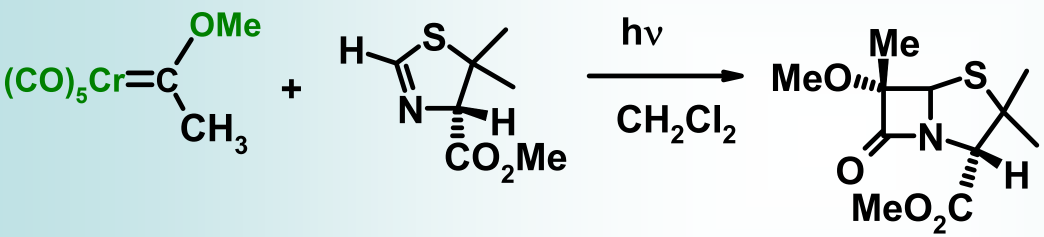
-many, many other synthetic examples -see

R Wulff, W.D. *Adv. Met. Org. Chem.* 1989, *1*, 209.
R Minatti, A.; Dötz, K.H. *Topics Organomet Chem* 2004, *13*, 123.

-other major ring formation reactions of Fischer carbenes is β-lactam synthesis



-for example

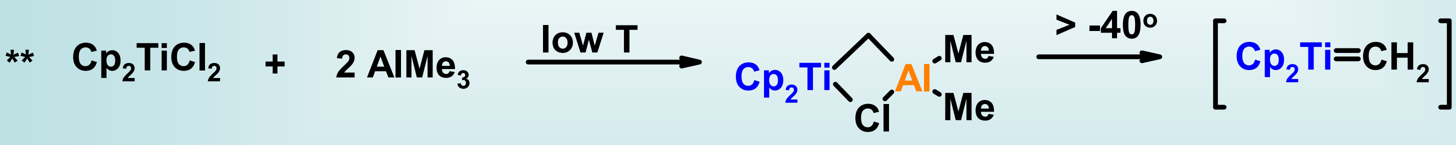


one isomer
penam derivative
(related to thienamycin)

R Hegedus, L.S. *Topics Organomet Chem* 2004,*13*, 157

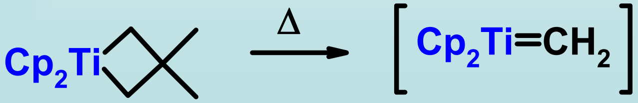
Schrock Carbenes (alkylidenes)

-somewhat newer - earliest version is....

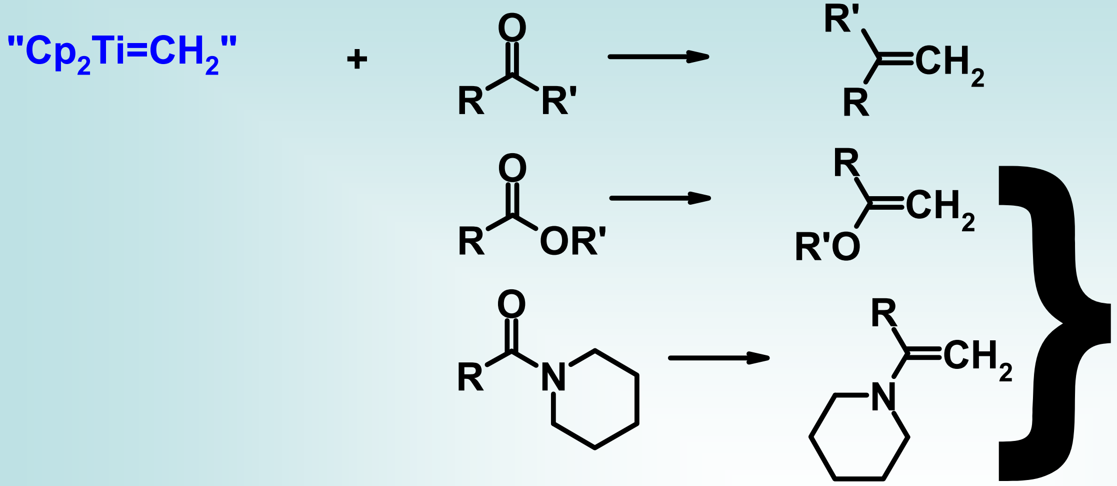


Tebbe reagent

or



-however one makes it....it is good at converting carbonyls into alkenes



not feasible with phosphorus ylide (Wittig) chemistry

-also works with carbonyls that are highly enolizable, whereas the Wittig reagent would simply deprotonate

R Hartley, R.C.; McKiernan, G.J. *J. Chem. Soc., Perkin Trans. 1* 2002, 2763

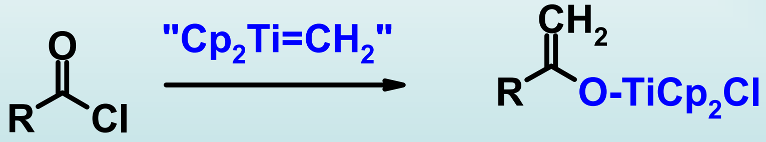
-alternative set of conditions, see:

R Grubbs, R.H.; Pine, S.H. "Comprehensive Organic Synthesis" 1991, vol 5, Ch 9.3 (p1115)

Problems - replacing $=CH_2$ with =CHR' gives a selectivity problem
$=C=CR_2$, =CHPh, =CHTMS do work, however

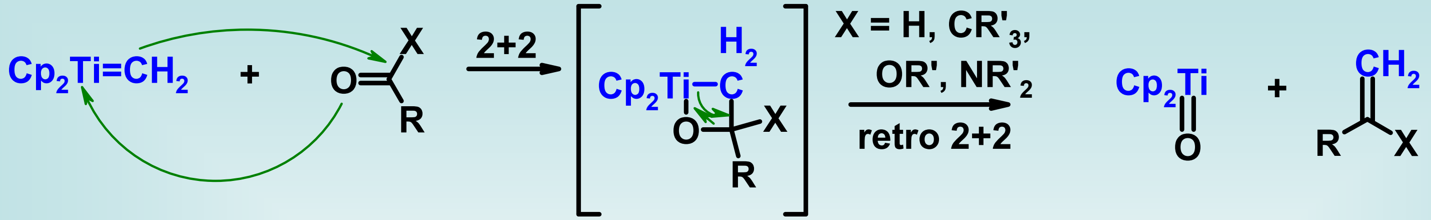
Nico Petasis (USC)

-acid chlorides do give enolates

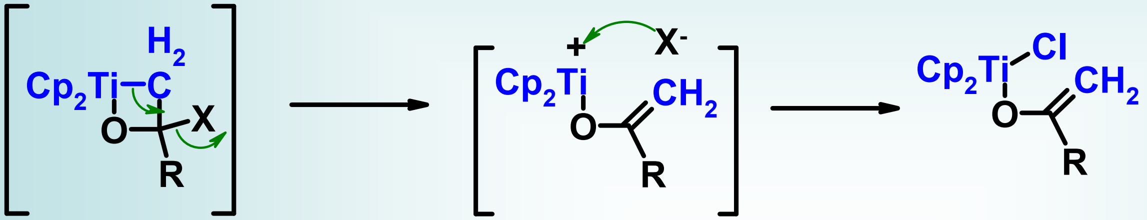


R Pine, S.H. *Org. React.* 1993, *43*, 1.
R Petasis, N.A. *Pure. Appl. Chem.* 1996, *67*, 667.

Mechanism - a metathesis type mechanism

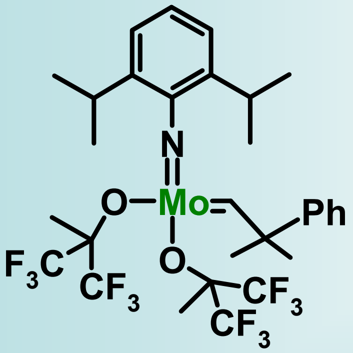


if X = Cl, it's a better leaving group, so...

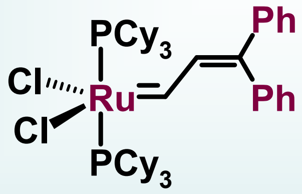


Metathesis of Alkenes

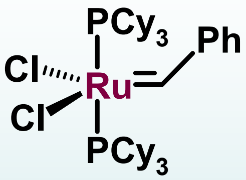
-these 2+2 / retrograde 2+2 cycloadditions become the dominant reaction pathway with several transition metal carbenes/alkylidenes



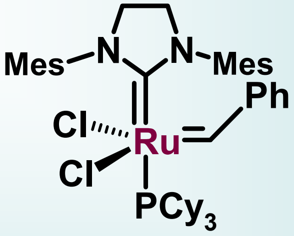
①



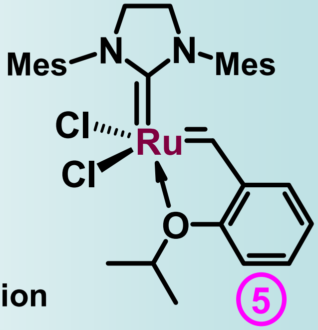
②



③ 1st generation



④ 2nd generation



⑤

Grubbs-Hoveyda

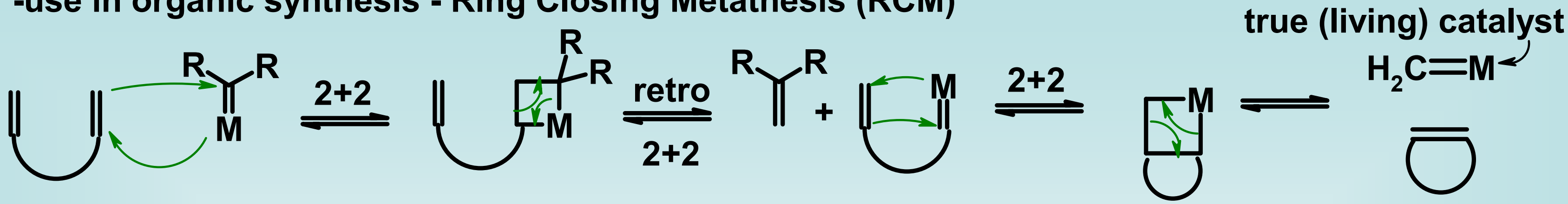
Schrock (pre)catalyst

-higher reactivity
-less stable, less easily handled
-not that functional group tolerant

Grubbs' (pre)catalysts

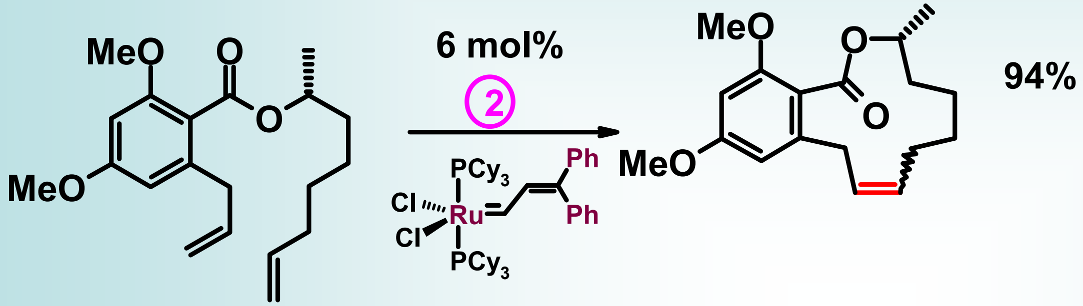
-more easily handled
-much more functional group tolerant
-less reactive (<u>4</u> is close)

-use in organic synthesis - Ring Closing Metathesis (RCM)

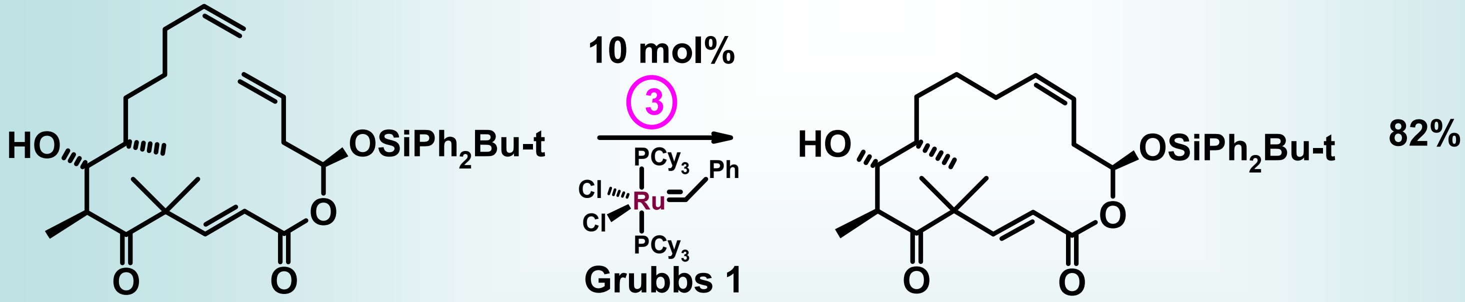


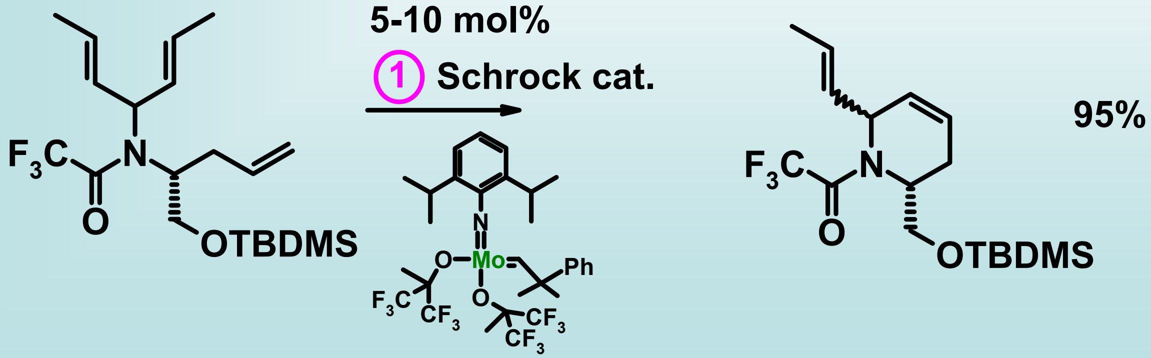
-has enormous synthetic utility

-can close rings of many sizes: normal to large - the 8-12 sizes are the toughest

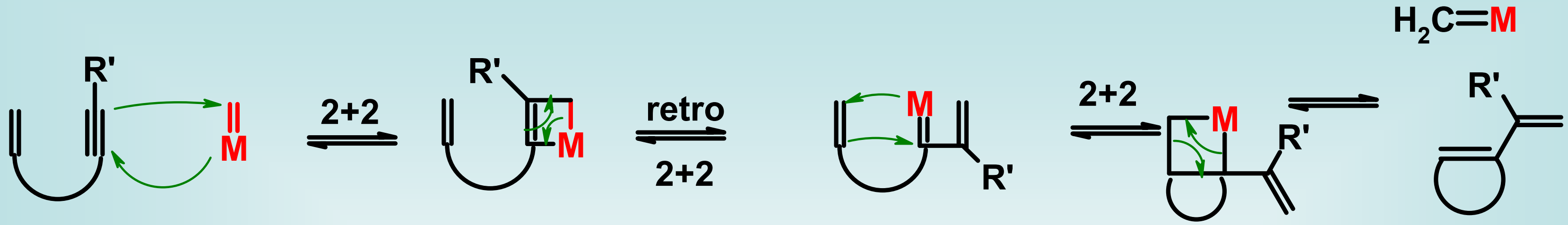


-this poor control over alkene stereochemistry is common

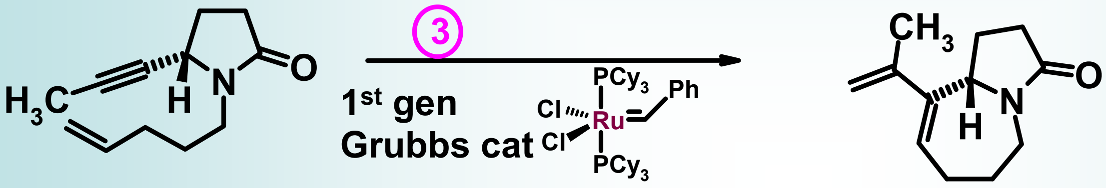




-one alkyne can be used in these ring closing metathesis reactions; get a diene as product



R Maifeld, S.V.; Lee, D. *Chem. Eur. J.* 2005, *11*, 6118
R Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* 2007, *63*, 3919.
R Mori, M. Adv. Synth. Catal. 2007, 349, 121. (in fact entire issue is on metathesis)
R Villar, H.; Frings, M.; Bolm, C. *Chemical Society Reviews* 2007, *36*, 55.



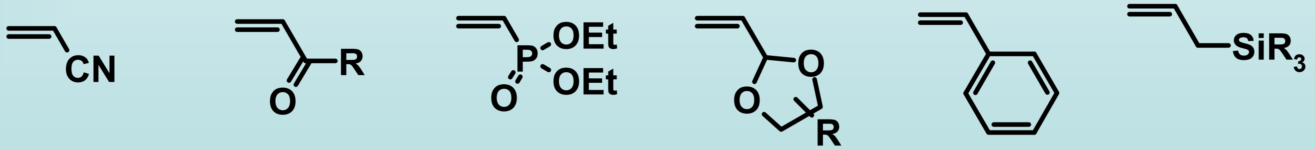
1st gen
Grubbs cat

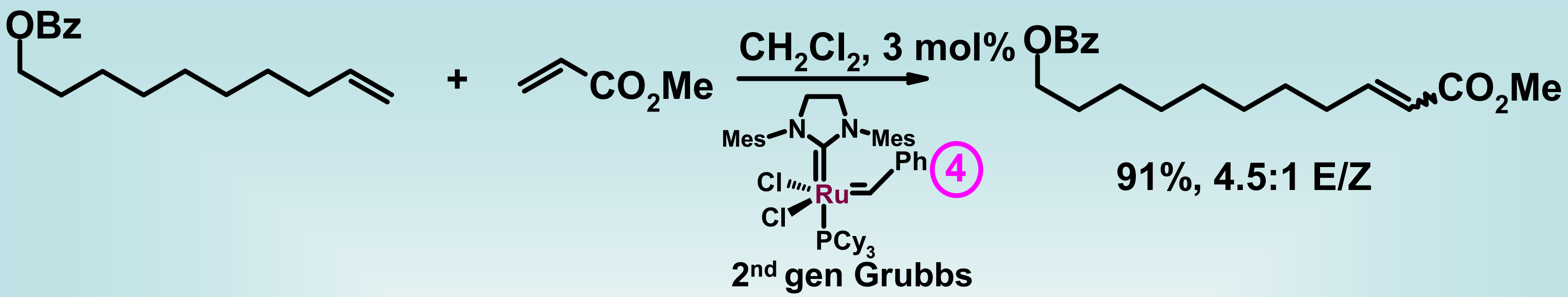
73%

R Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* 2007, *63*, 3919.
R Mori, M. *Adv. Synth. Catal.* 2007, *349*, 121 (entire issue is on metathesis)
R Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* 2007, *36*, 55.
R Maifeld, S. V.; Lee, D. Chem.-Eur. J. 2005, *11*, 6118.

Cross Metathesis - Intermolecular

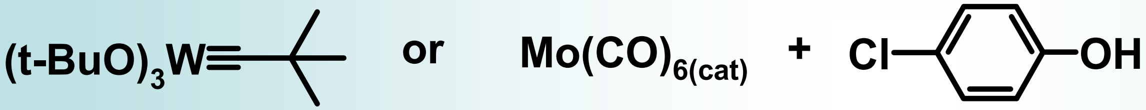
-metathesis of two alkenes can be intermolecular, but there is normally a problem with selectivity
-in some cases, an alkene can be chosen such that metathesis with itself is slowed down to almost zero
-in these cases, it is possible to do cross-metathesis with a second, unhindered alkene
-the 'slow' alkene is normally either $H_2C{=}CH$-EWG or $H_2C{=}CH$-BIG





R Connon, S.J.; Blechert, S. *Angew. Chem. int. Ed. Engl.* 2003, *42*, 1900.

Note: There is much work and progress in the RCM of diynes, using alkylidyne (carbyne) intermediates



R Furstner, A.; Davies, P.W. *Chem. Commun.* 2005, 2307.

Ring Closing Metathesis reviews - many, many, many - selected ones include..

R Hoveyda, A. H.; Zhugralin, A. R. *Nature* 2007, *450*, 243.
R Conrad, J. C.; Fogg, D. E. *Current Organic Chemistry* 2006, *10*, 185.
R Grubbs, R. H.; Trnka, T. M. 'Ruthenium in Organic Synthesis' 2004,153
R Mulzer, J.; Oehler, E. *Top. Organomet. Chem.* 2004, *13*, 269
R Grubbs, R. H *Tetrahedron* 2004, *60*, 7117
R Hoveyda, A.H.; Schrock, R.R, *Angew. Chem. Int. Ed. Engl.* 2003, *42*, 4592 (Mo)
R Hoveyda, A.H.; Schrock, R.R *Chem.-Eur. J.* 2001, *7*, 945 (asymmetric)
R Furstner, *A. Angew. Chem. Int. Ed. Engl.* 2000, *39*, 3012.
R Jafarour, L.; Nolan, S.P. *J. Organomet. Chem.* 2001, *617-618*, 17.
R Tanka, T.M.; Grubbs, R.H. *Acc. Chem. Res.* 2001, *34*, 18.
R Schrock, R.R., *Tetrahedron* 1999, *55*, 8141. (Mo)