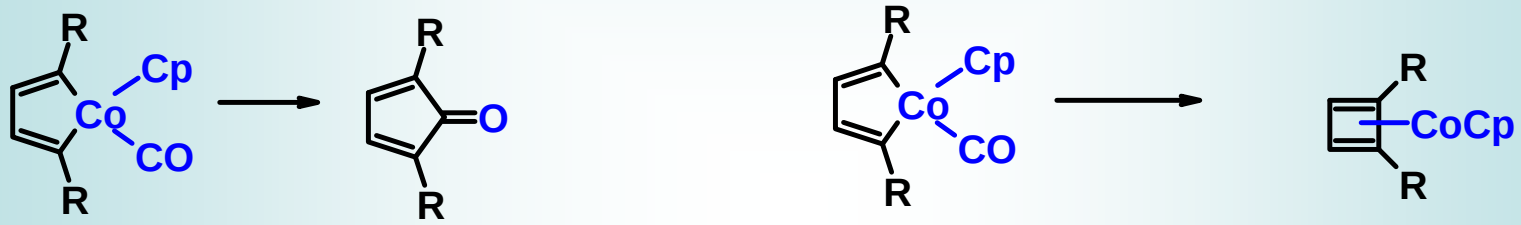
3. Interrupting the 2+2+2

-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:

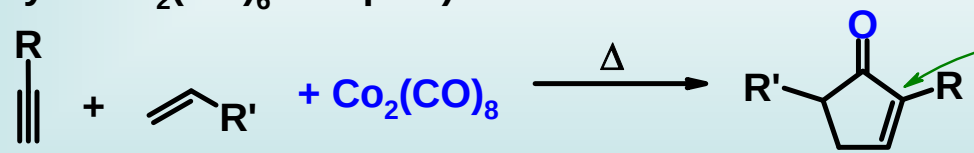


(Fe : Knolker, H.J.)

-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.,

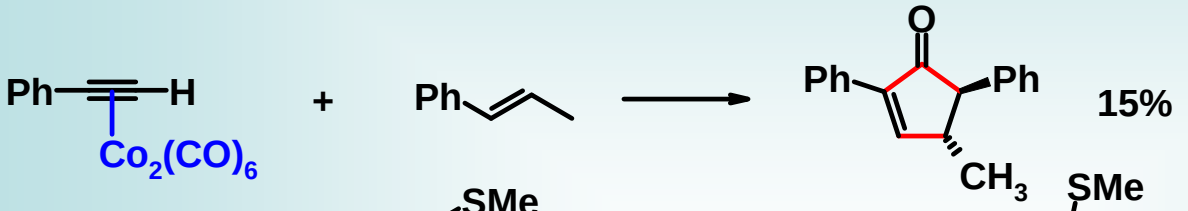


Intermolecular Cases

-no particular constraints on the alkyne
-if you have an unsymmetrical alkyne, larger groups end up next to C=O, as in

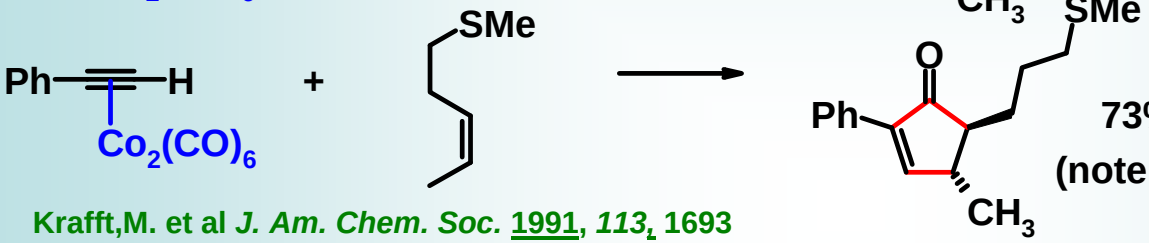
Alkene Partner

-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%

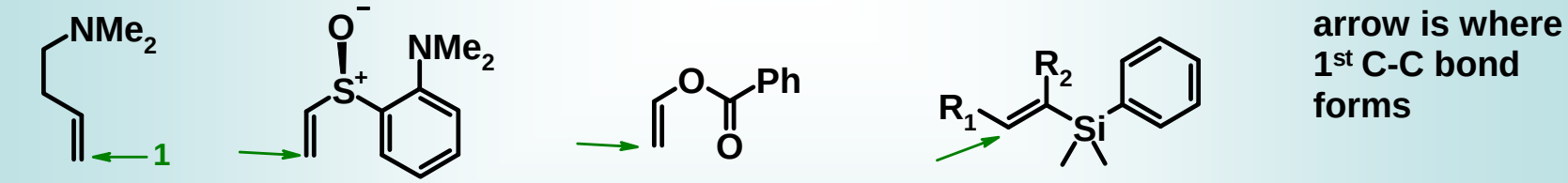
ordinary alkene



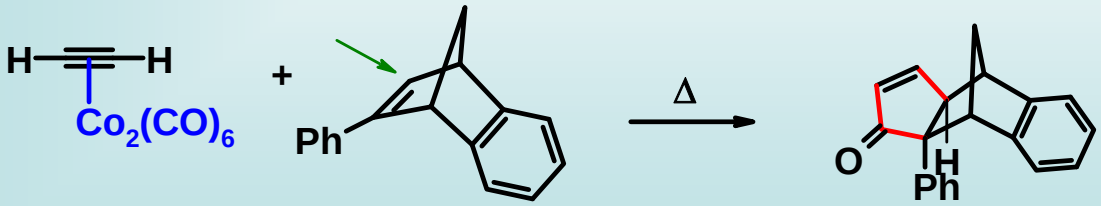
73%
(note: trans)

coordinating substit.

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

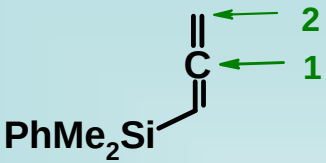


arrow is where 1st C-C bond forms



bridged bicyclic alkene
(non β-hydride)

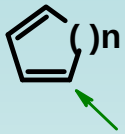
high %



Cazes (no β-H)

especially
n = small

even n = normal
with mild conditions



"no β-H"

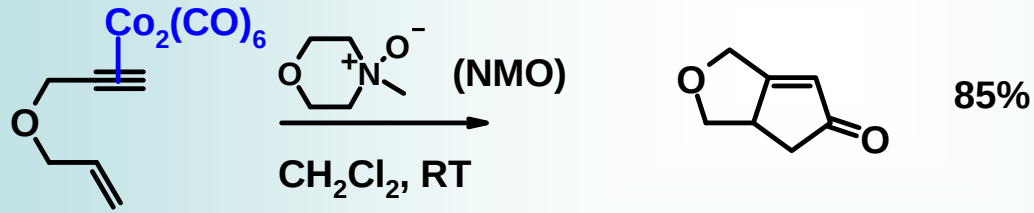
Reviews focussing on intermolecular reactions

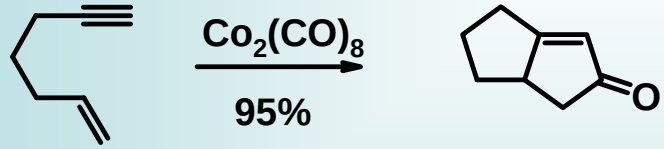
R Gibson, S.E. et al *Angew. Chem. Int. Ed.* 2005, *44*, 3022.
R Laschat, S. *Synlett* 2005, 2547.

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

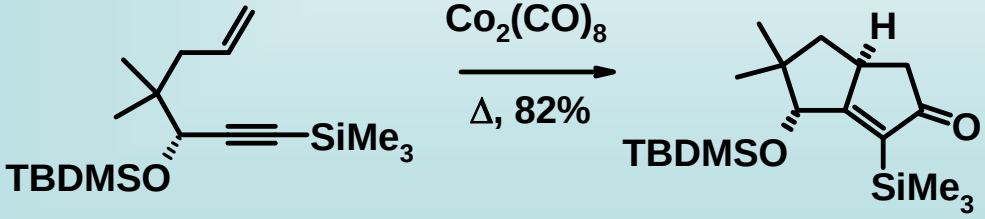
Intramolecular Cases

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





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

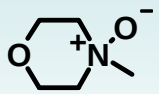


gem dimethyl or Thorpe-Ingold effect

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

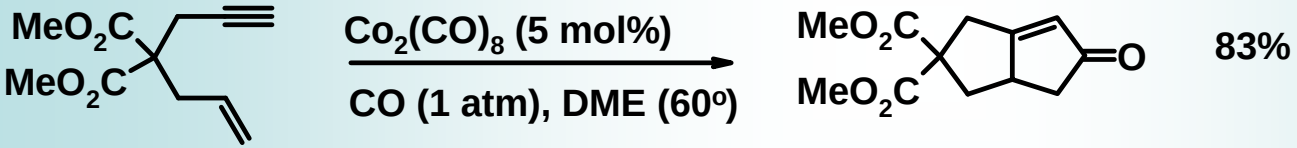
i.e., polar aprotic solvents (CH_3CN, DME )

-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)



83%

-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	

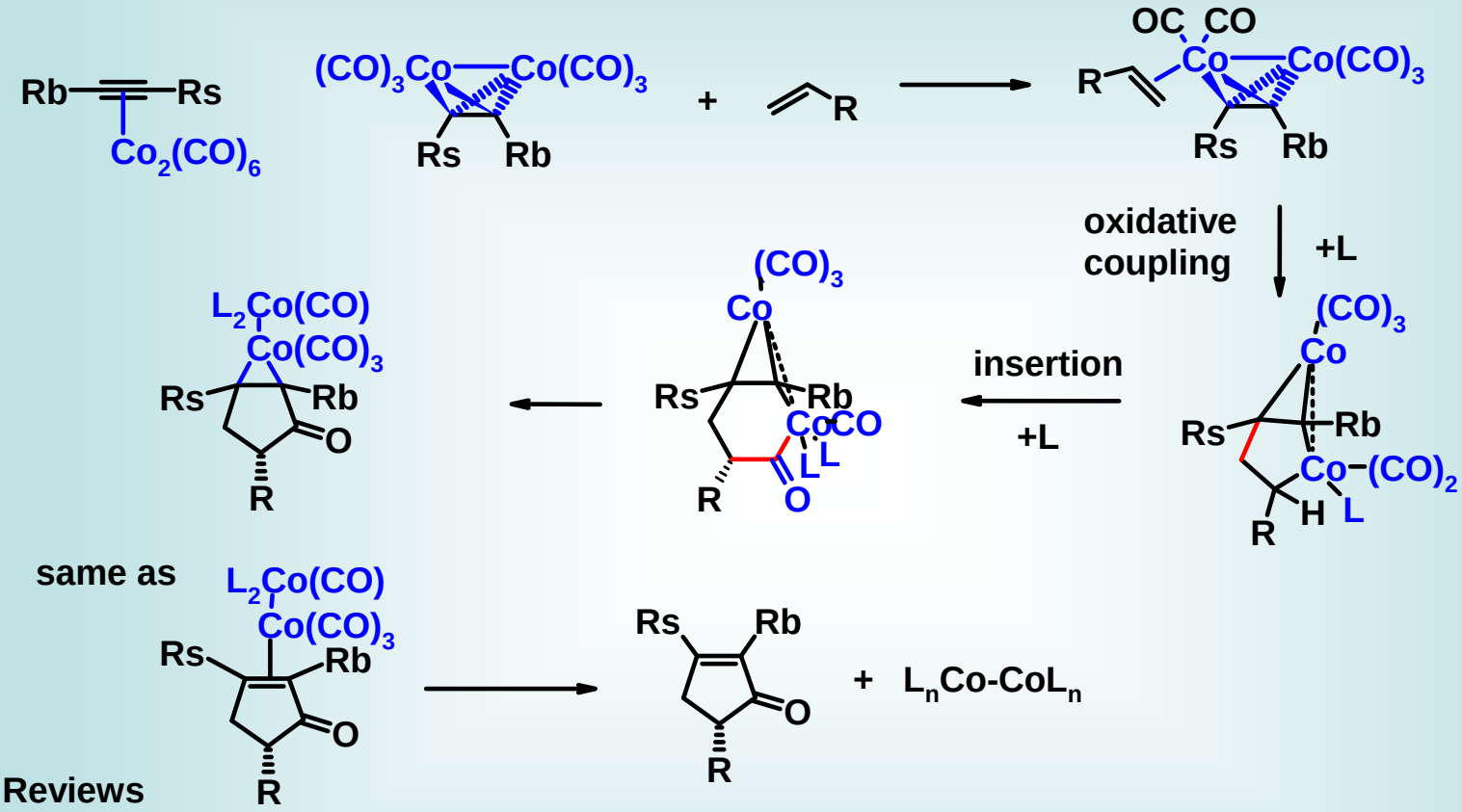
Zr^{II}	4
Fe^o, hν	4
Co nanoparticles	2
Co^I	1
W	1

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'

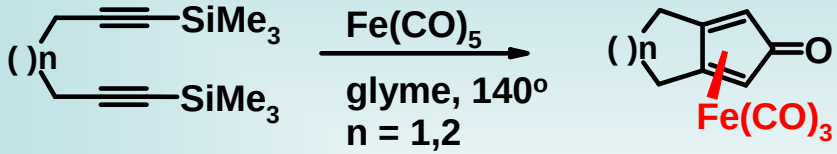


Reviews

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^o and product is the iron complex



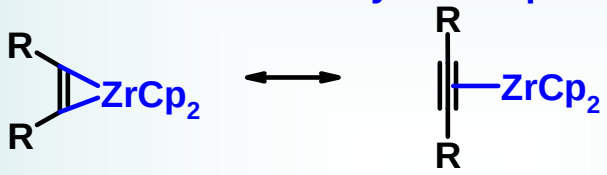
ca. 80%

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

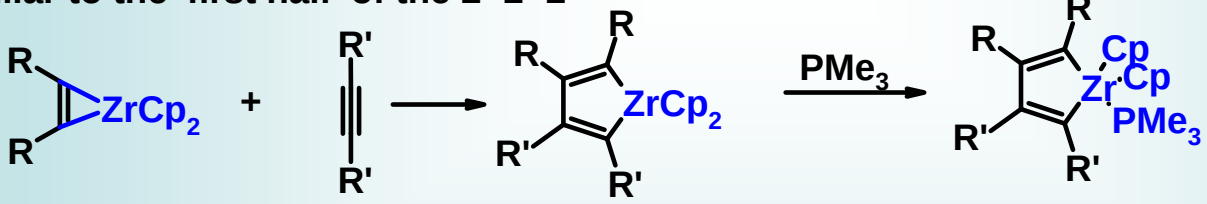
-decomplexation is not straight-forward, because cyclopentadienone is unstable (anti-aromatic)

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

-compounds like



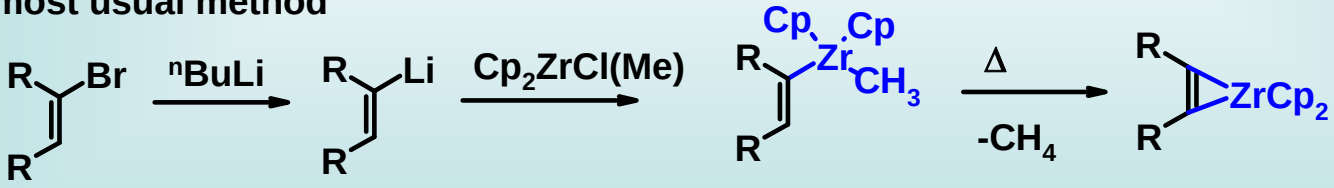
-also react with alkynes, alkenes, nitriles, to form C-C bonds by oxidative coupling process, similar to the 'first half' of the 2+2+2



-can be isolated as the PMe_3 adduct

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

-most usual method

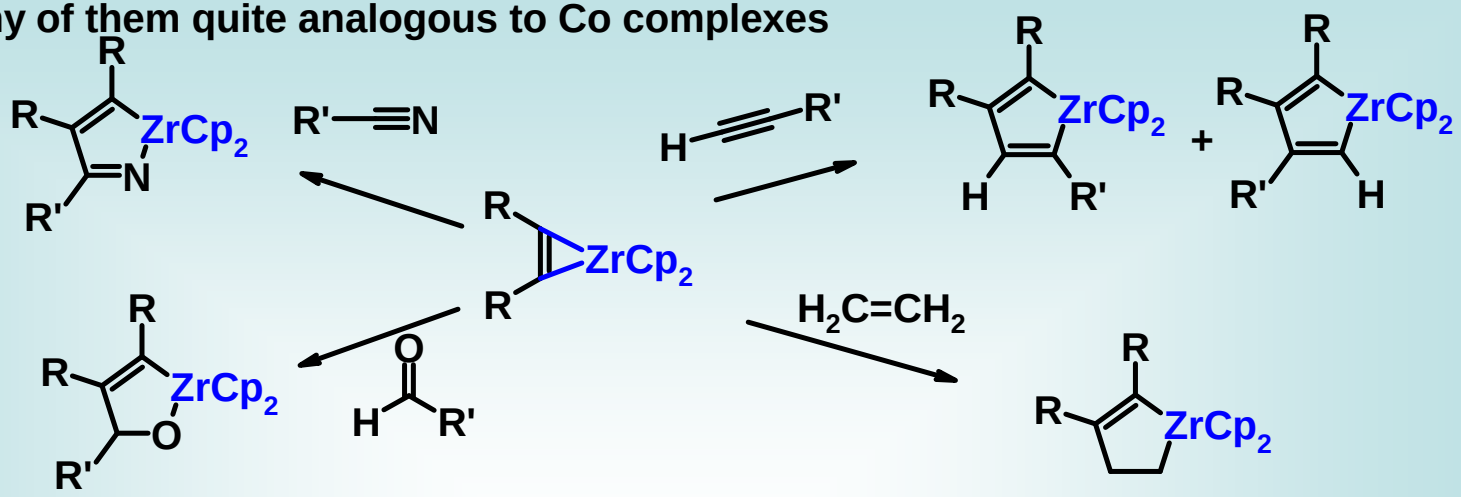


R cannot be H,

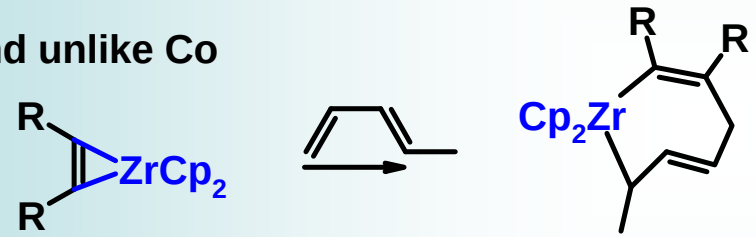
also made this way

Reactions Encountered

-many of them quite analogous to Co complexes

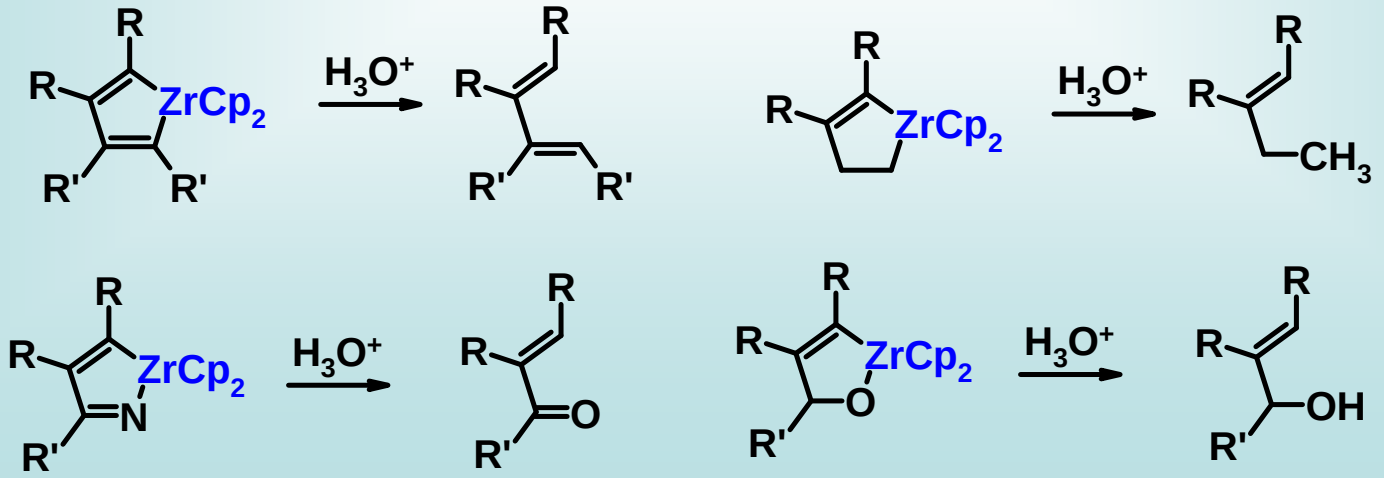


and unlike Co

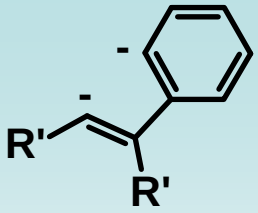


-are further reaction possible? - YES

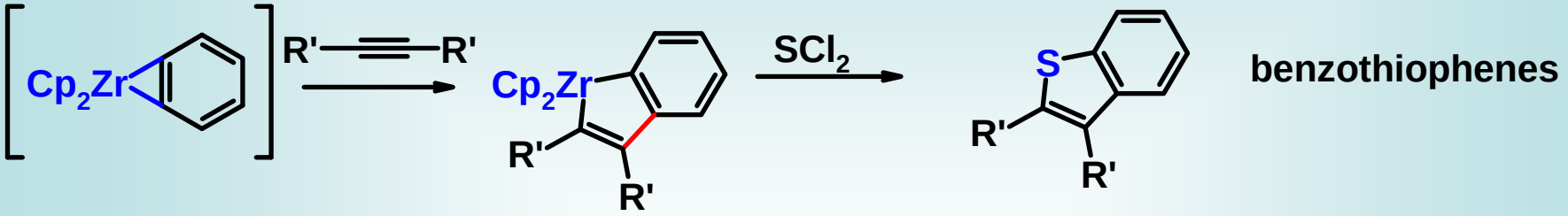
-most common is hydrolysis



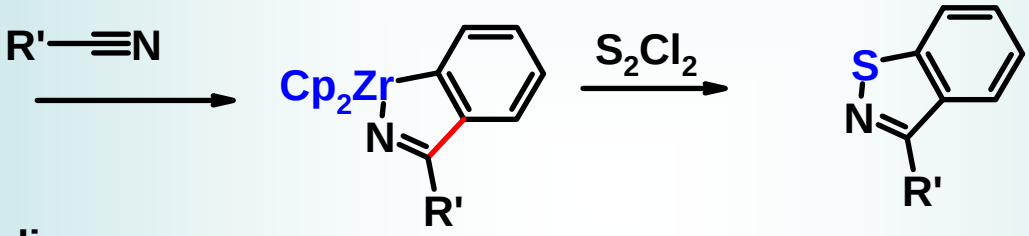
-due to electronegativity difference between
C and Zr, there's a tendency for these to react like



-other reactions -with sulphur monochloride or dichloride

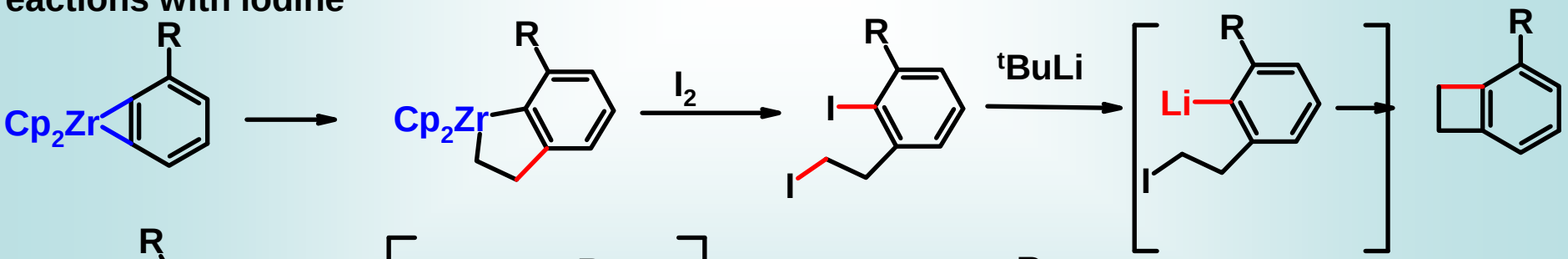


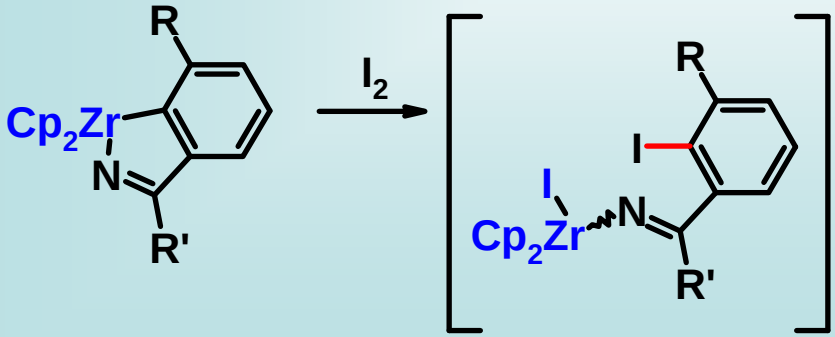
benzothiophenes



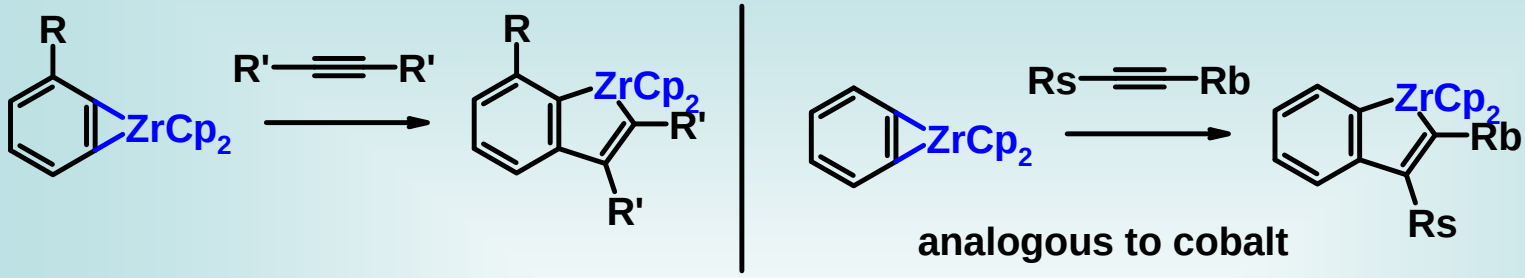
benzothiazoles

-reactions with iodine

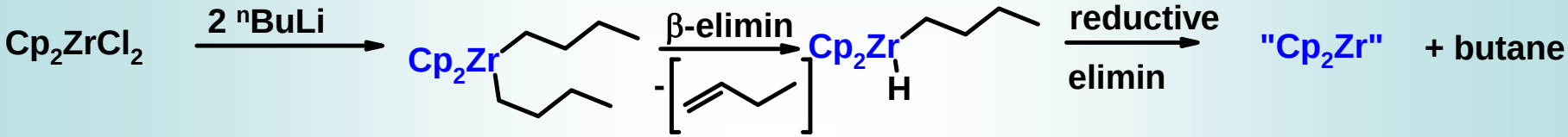


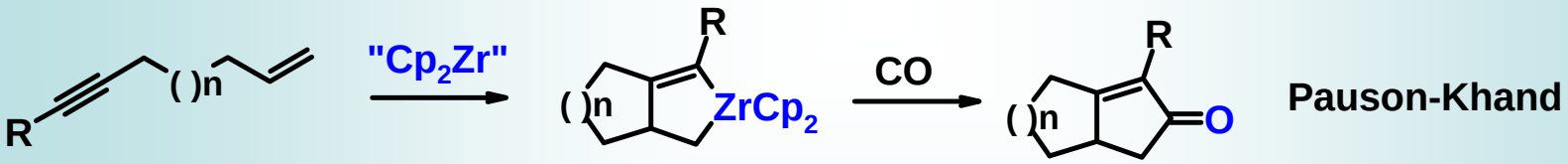


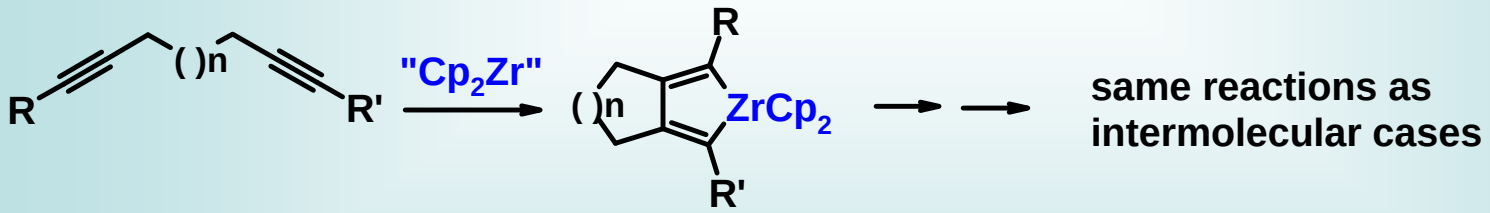
Regiochemistry in benzyne reactivity



Intramolecular cases - E.I. Negishi







see

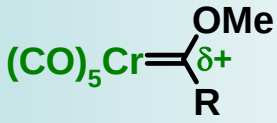
R Negishi, E.; Takahashi, T. *Bull. Chem. Soc. of Jpn.* 1998, *71*, 755.
R Majoral, J.-P. et al *Coord. Chem. Rev.* 1998, *178-80*, 145 (main group elements)
R Negishi, E. *Acc. Chem. Res.* 1994, *27*, 124.
R Buchwald, S.L.; Nielsen, R.B. *Science* 1993, *261*, 1696.
R Buchwald, S.L. *Chem. Rev.* 1988,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

Carbenes

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

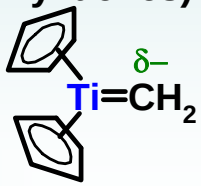
-structurally discrete carnes 'officially' fall into two types, characterized by their reactivity
-I will arbitrarily add a third class

Fischer Type Carbenes



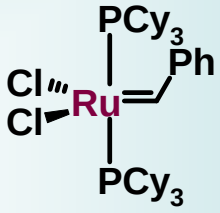
-mostly Cr group (Cr, Mo, W), or Fe group
-stabilized by heteroatom (O here)
-reactivity - electron poor at C

Schrock Type Carbenes (alkylidenes)



-early transition metal
-electron rich at carbon

Methesis Carbenes



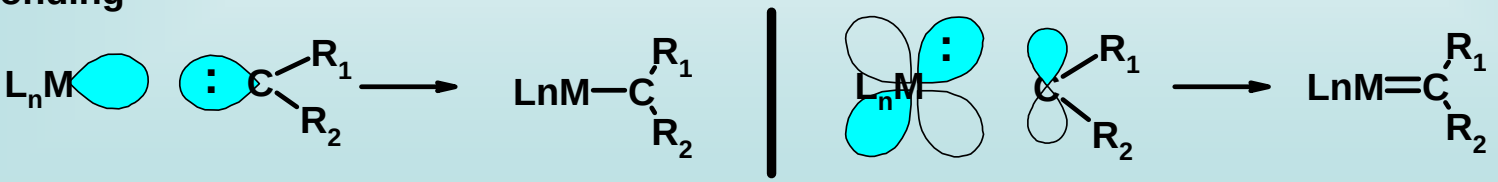
- early development by Schrock, so often lumped in with Schrock carbenes for convenience

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

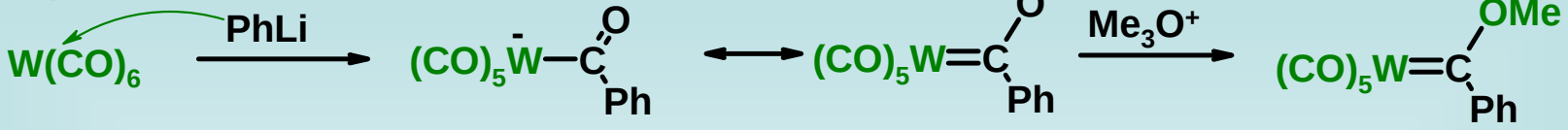
Fischer Carbenes

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

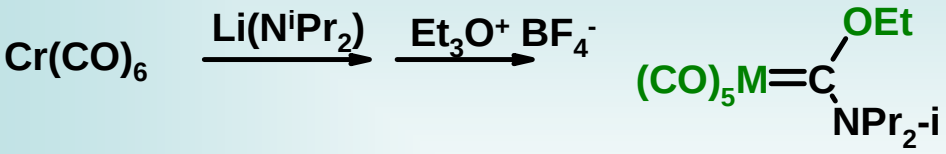
Bonding



Preparation

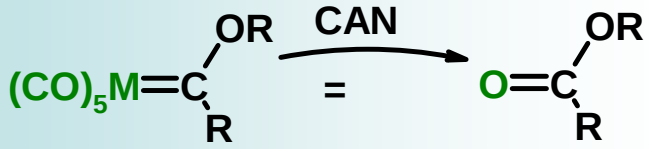


-nucleophiles mostly alkyllithiums, but don't absolutely have to be C based



Reactions of Fischer Carbenes

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



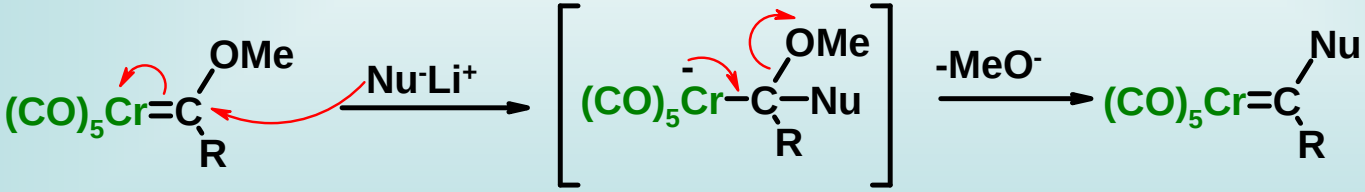
-can actually do the transformation with Ce^{IV}

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

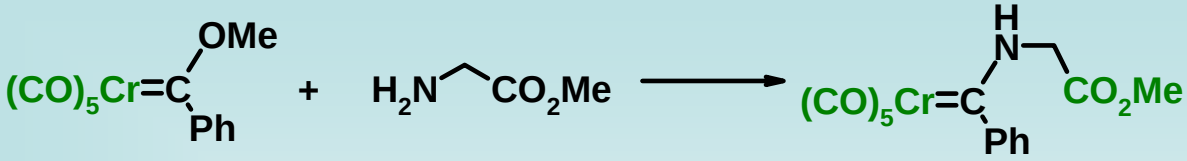


nucleophiles include

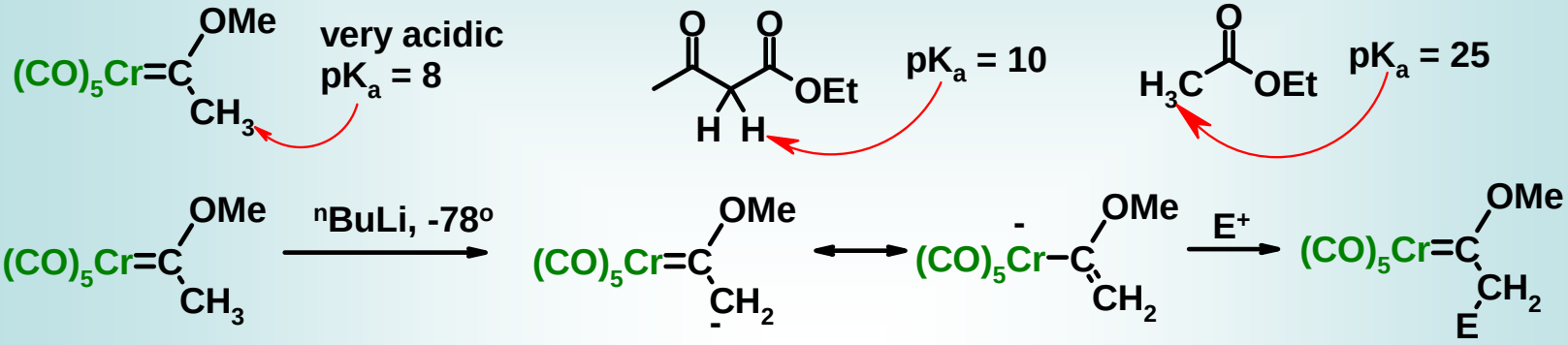
organolithiums RLi

amines R'_2NH

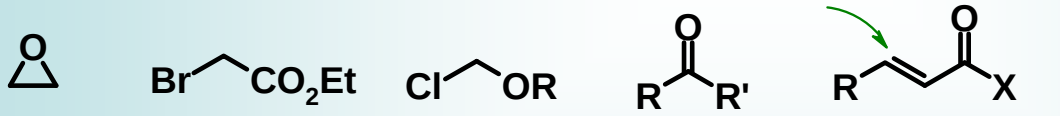
mercaptans RSH



b) Generation of α-Anion and Electrophile capture

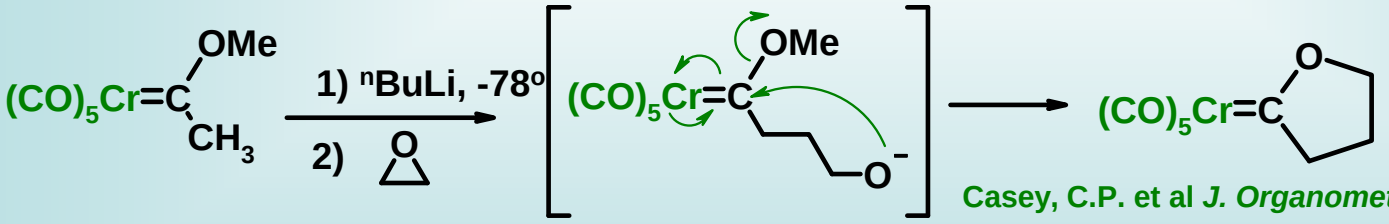


-anion is so stabilized that it's a fairly weak nucleophile; therefore only captures more reactive electrophiles



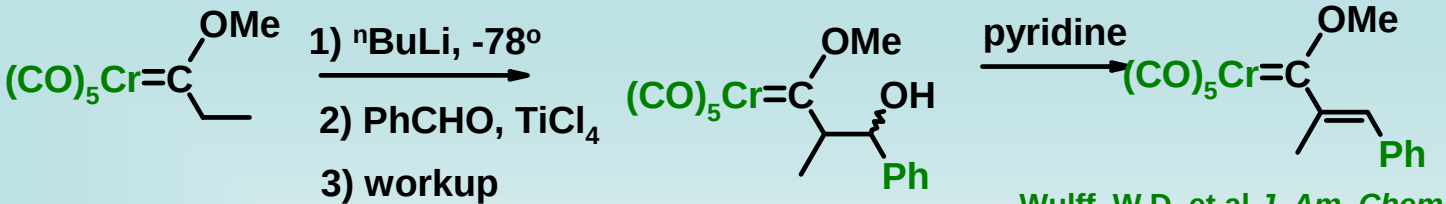
(Michael acceptor)

-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



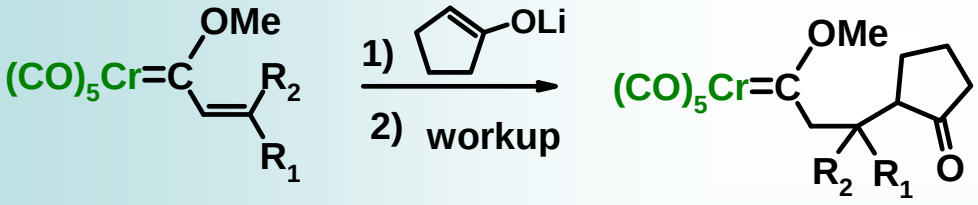
Wulff, W.D. et al *J. Am. Chem. Soc.* 1985, *107,* 503.

-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.....

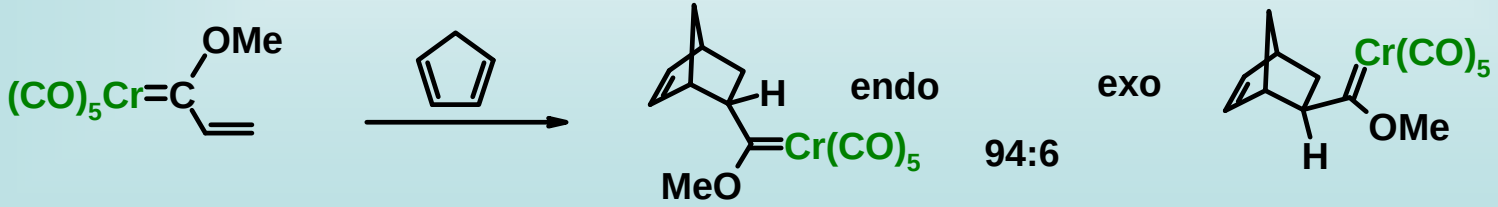


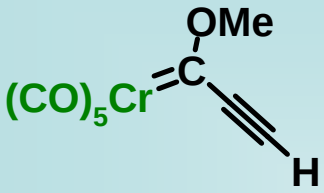
Nakamura, E. *J. Am. Chem. Soc.* 1993, *115*, 9015.

-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



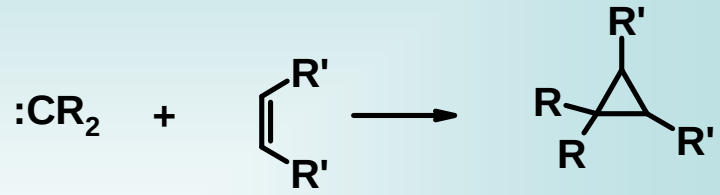


also partcicpate

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.

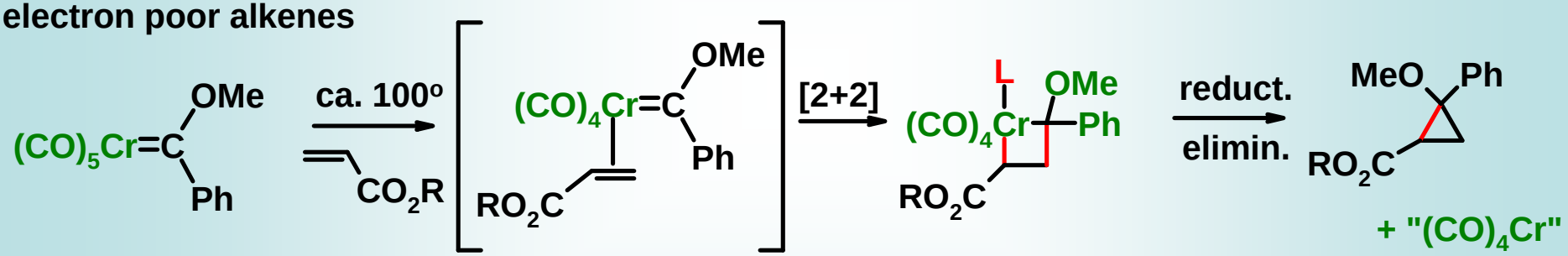
Cyclopropanation with Alkenes

-typical reaction of carbenes in organic chemistry

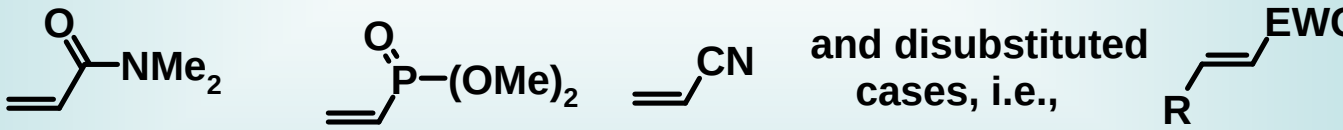


-may also be done with discrete organometallic complexes, with either electron poor or electron rich alkenes - probably by two different mechanisms

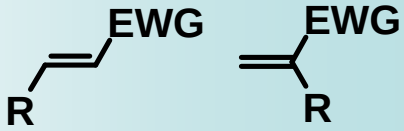
electron poor alkenes



-works with

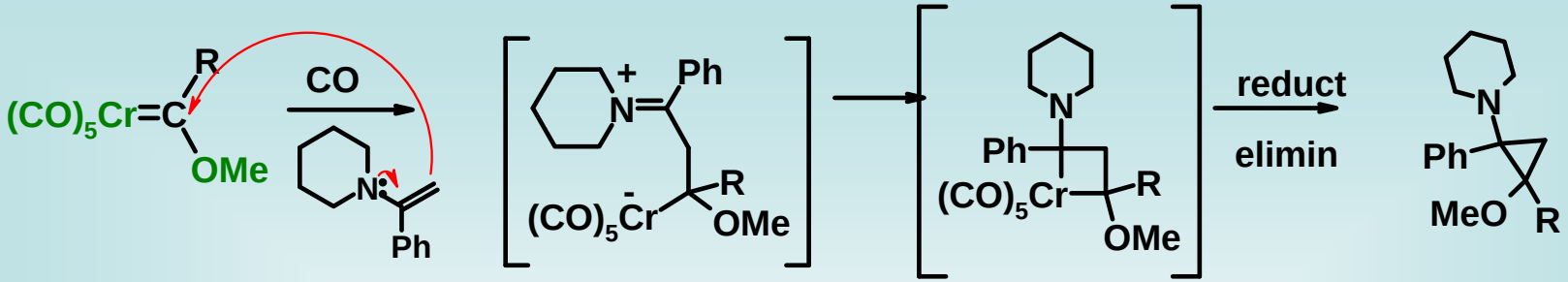


and disubstituted cases, i.e.,

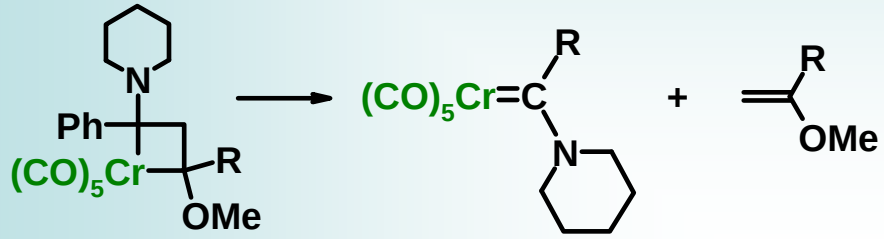


R Reibig, H.-U. "Organometallics in Organic Synthesis", V2, 1987, p.31
R Dotz, K.H. *Angew. Chem. Int. ed. Engl.* 1984, *23*, 587.
R Wu, Y,-T., Kurahashi, T., De Meijere, A. *J. Organomet. Chem.* 2005, *690*, 5900.
R Barluenga, J.; Rodríguez, F.; Fañanás, F.J.; Flórez, J. *Top. Organomet. Chem.* 2004,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

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

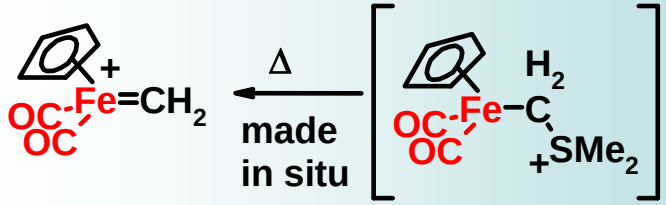


-reaction done under CO atmosphere to suppress alkene metathesis



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

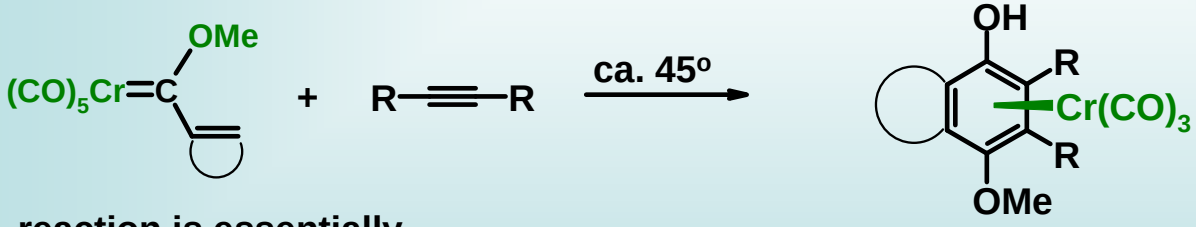
-see R Helquist, P. *Adv. Met. Org. Chem.* 1991, *2*, 143



Carbene-Alkyne Cycloaddition

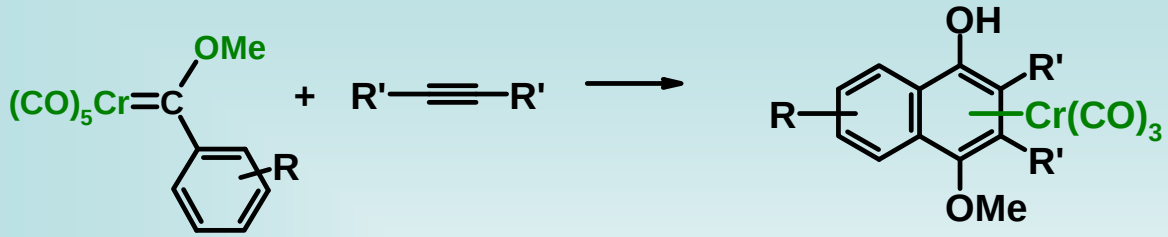
-probably most important type of rxn of Fischer carbenes; many uses in organic synthesis

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

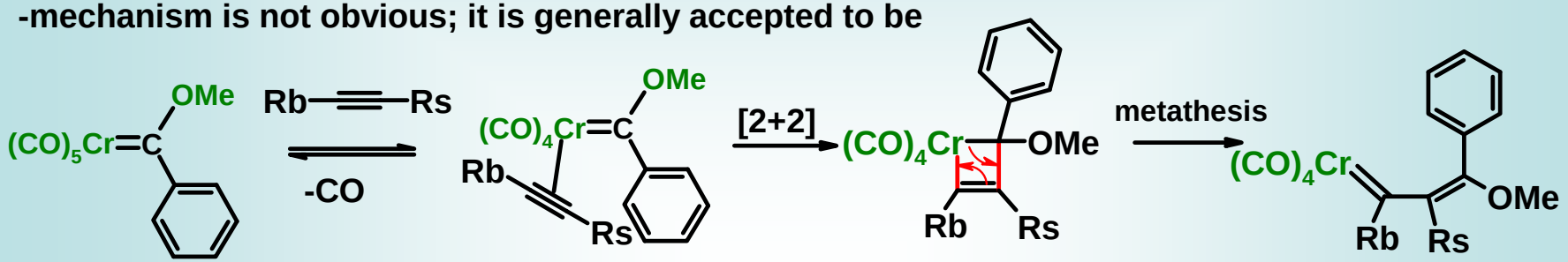


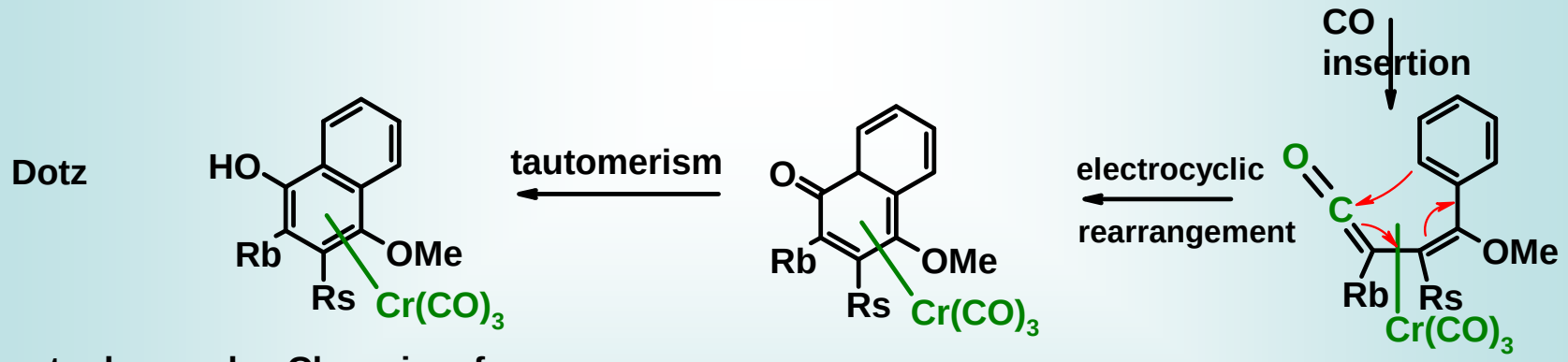
reaction is essentially

-this process also occurs on aryl substituted carbenes

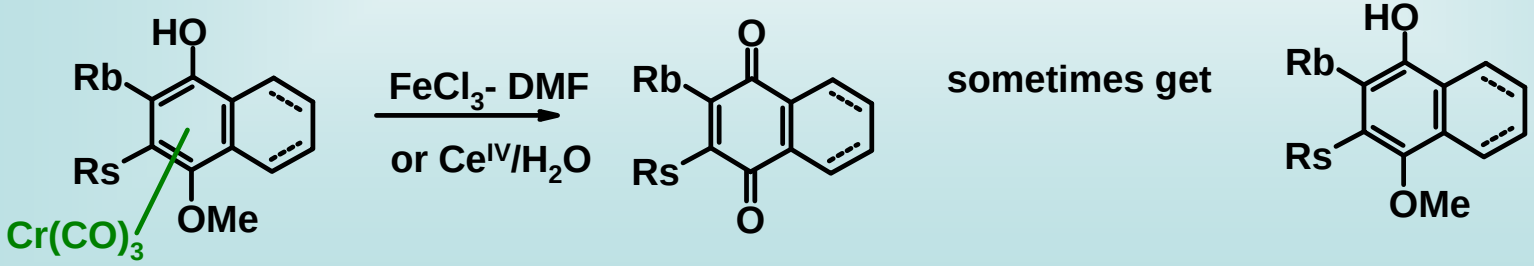


-mechanism is not obvious; it is generally accepted to be

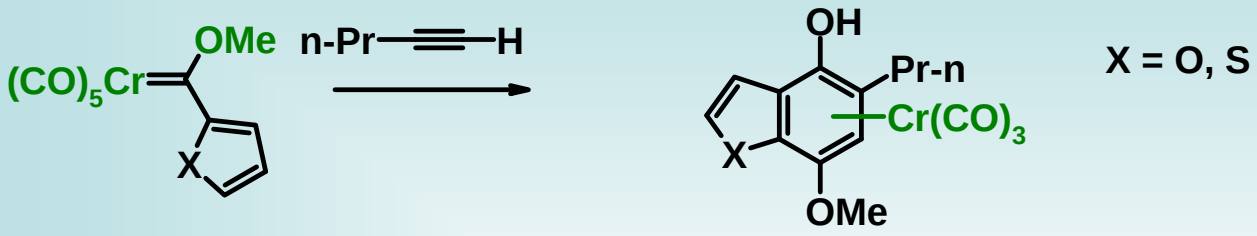




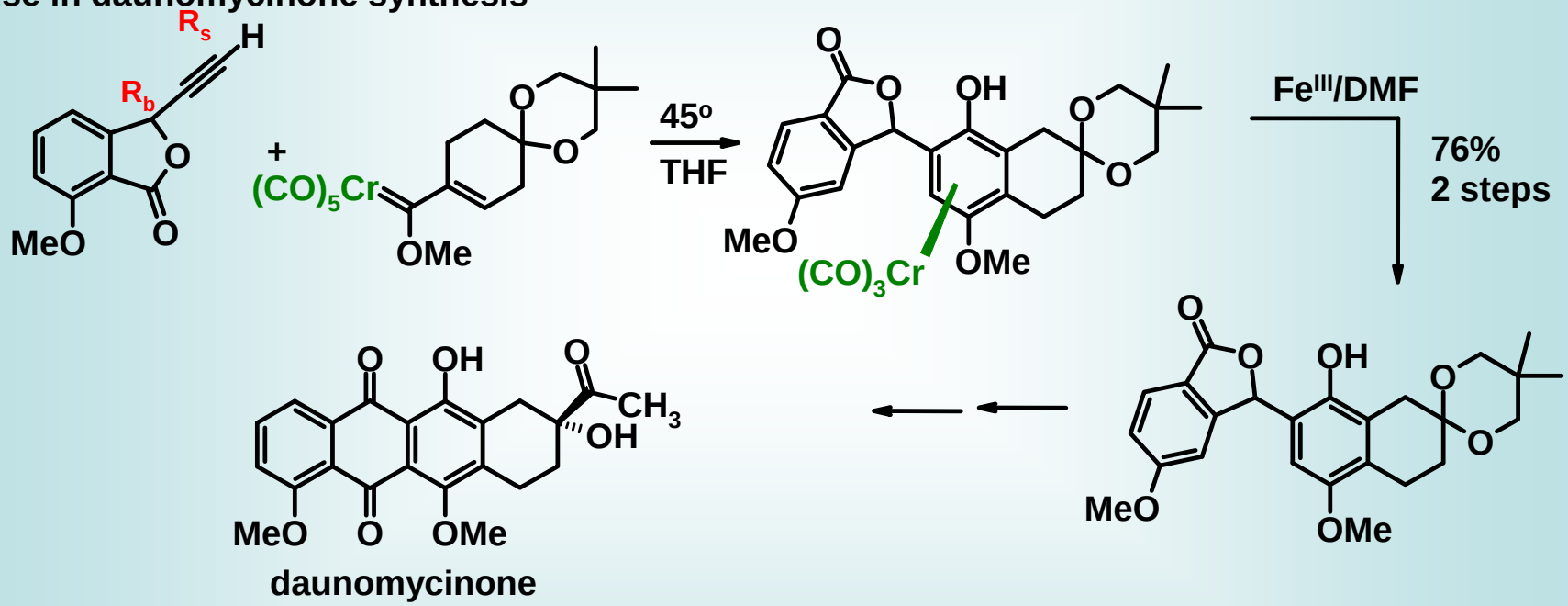
-easy to decomplex Chromium from arene



-aromatic heterocycles participate as well



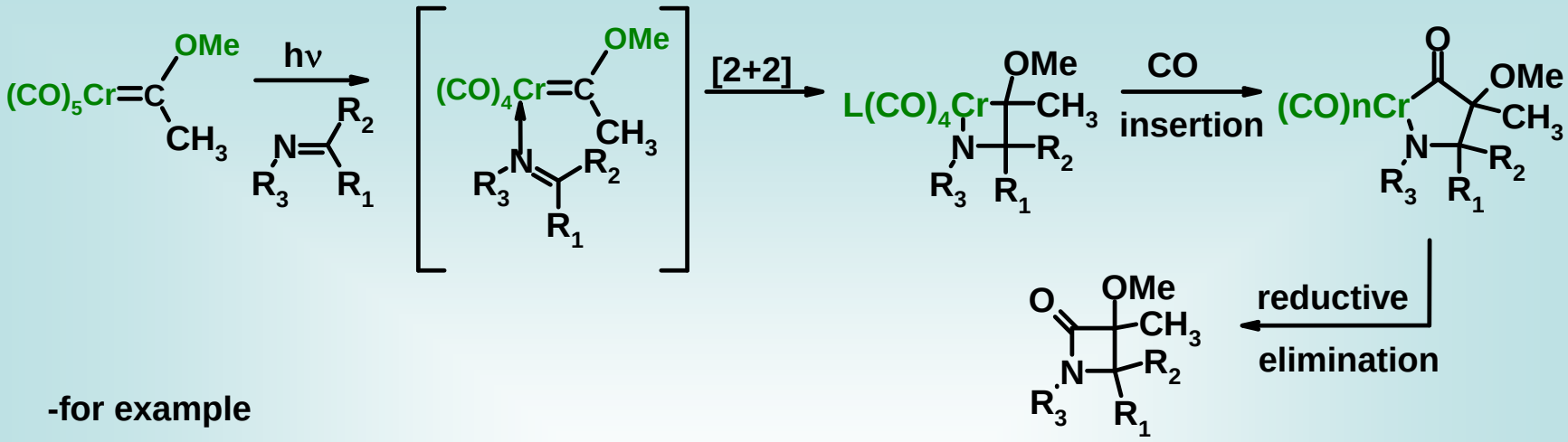
-use in daunomycinone synthesis



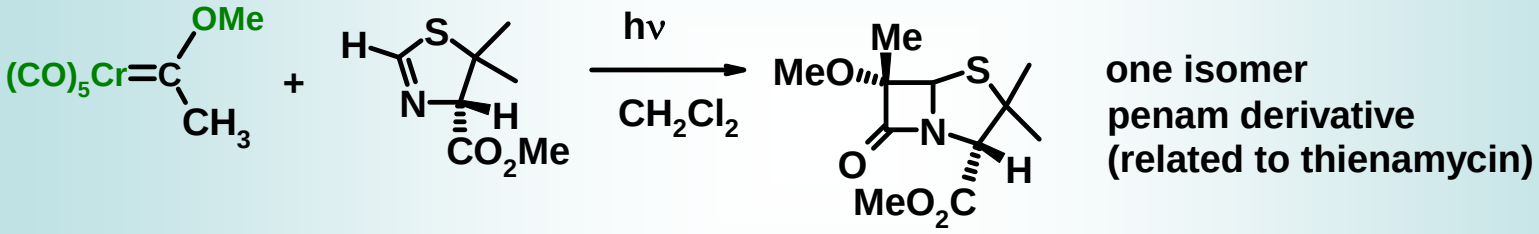
-many, many other synthetic examples -see

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

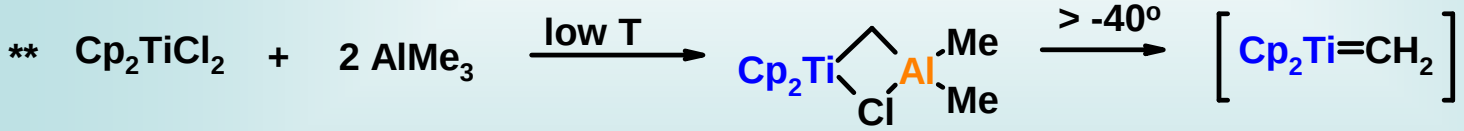


one isomer
penam derivative
(related to thienamycin)

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

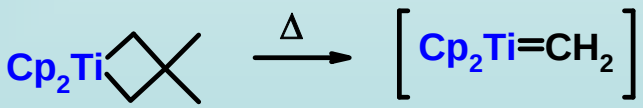
Schrock Carbenes (alkylidenes)

-somewhat newer - earliest version is....

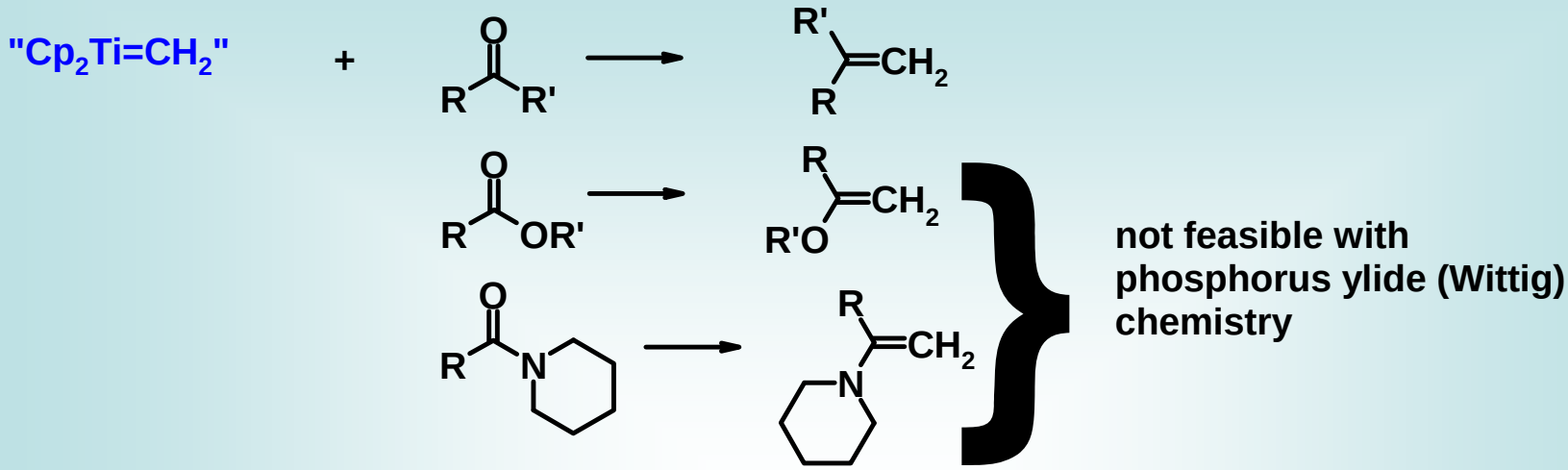


Tebbe reagent

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:

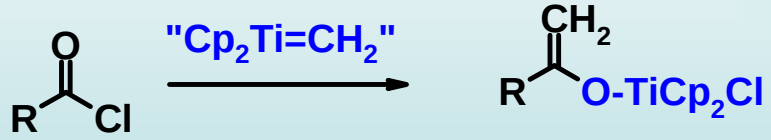
R Grubbs, R.H.; Pine, S.H. "Comprehensive Organic Synthesis" 1991, vol 5, Ch 9.3 (p1115)

Problems - replacing $=CH_2$ with =CHR' gives a selectivity problem

$=C=CR_2$, =CHPh, =CHTMS do work, however

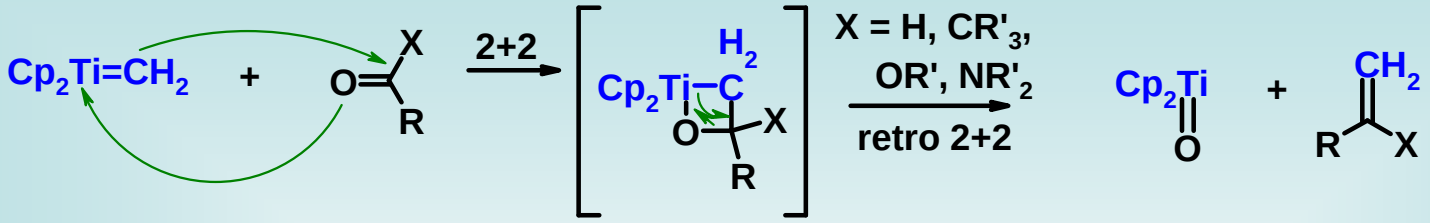
Nico Petasis (USC)

-acid chlorides do give enolates

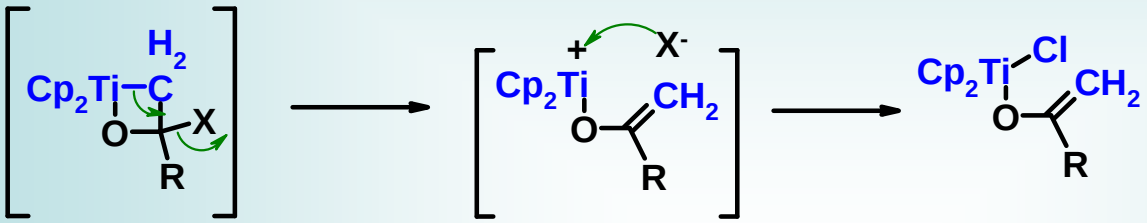


R Pine, S.H. *Org. React.* 1993, *43*, 1.
R Petasis, N.A. *Pure. Appl. Chem.* 1996, *67*, 667.

Mechanism - a metathesis type mechanism

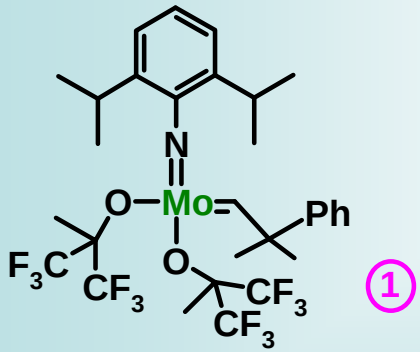


if X = Cl, it's a better leaving group, so...



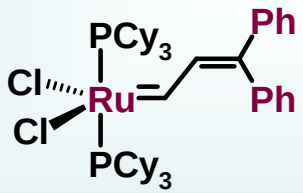
Metathesis of Alkenes

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

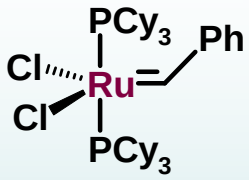


① **Schrock (pre)catalyst**

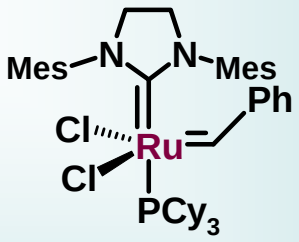
-higher reactivity
-less stable, less easily handled
-not that functional group tolerant



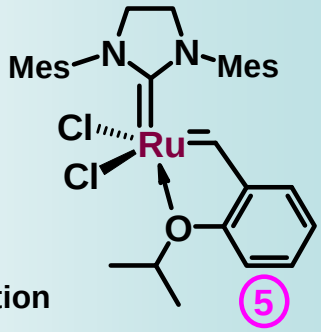
② **Grubbs' (pre)catalysts**



③ **1st generation**



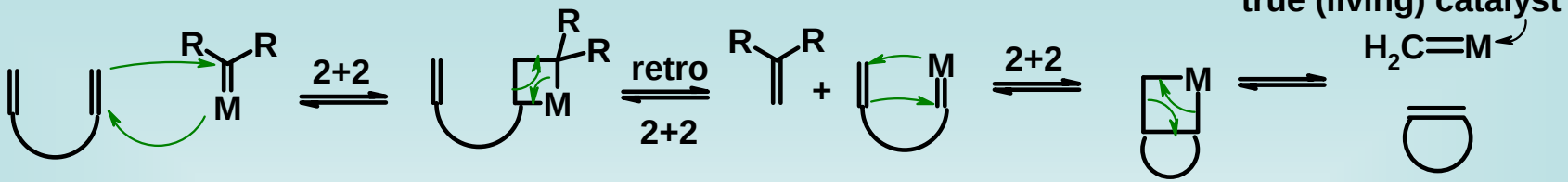
④ **2nd generation**



⑤ **Grubbs-Hoveyda**

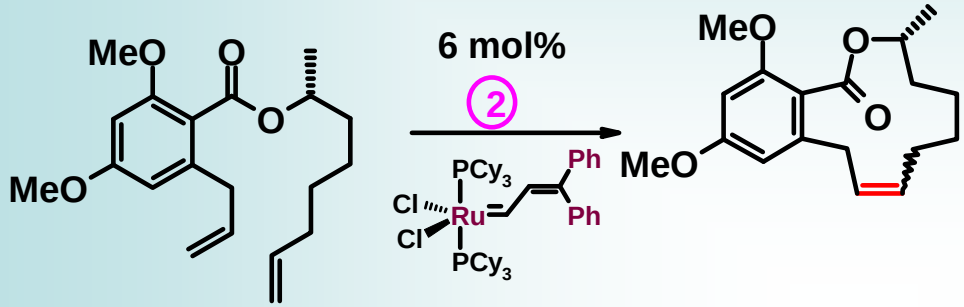
-more easily handled
-much more functional group tolerant
-less reactive (4 is close)

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



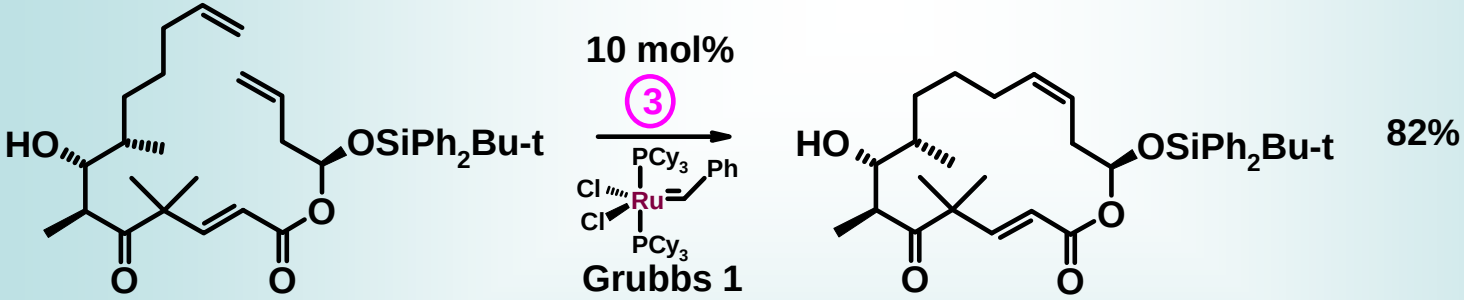
-has enormous synthetic utility

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

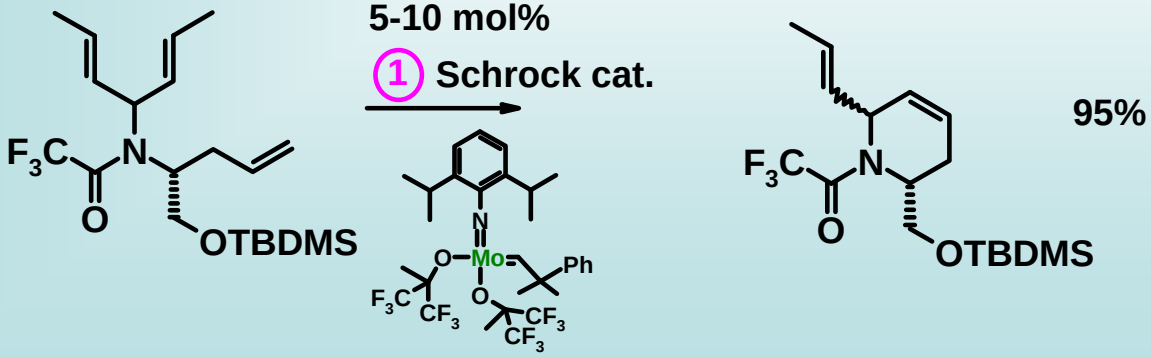


94%

-this poor control over alkene stereochemistry is common

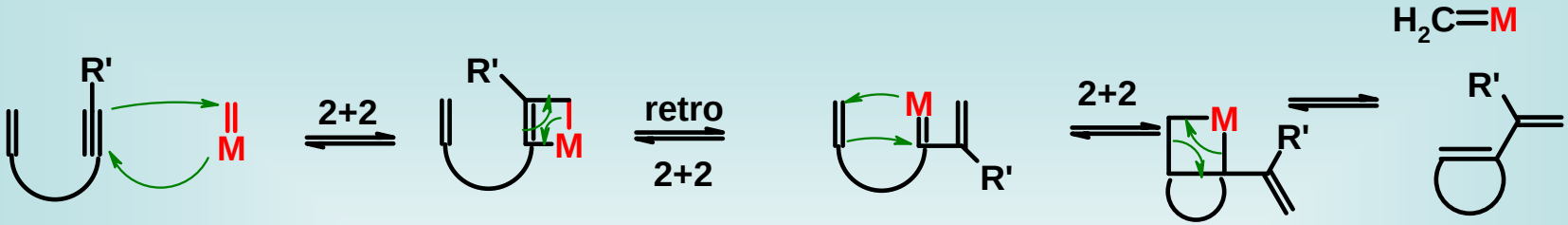


82%

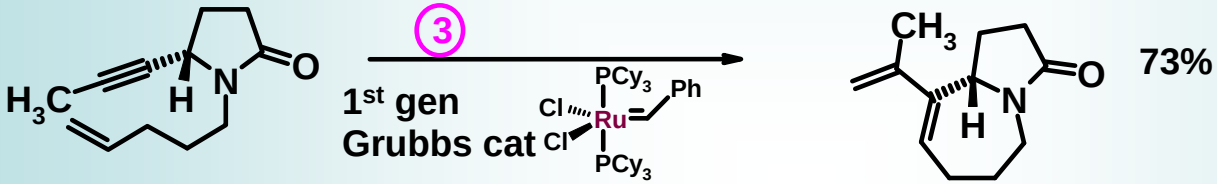


95%

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



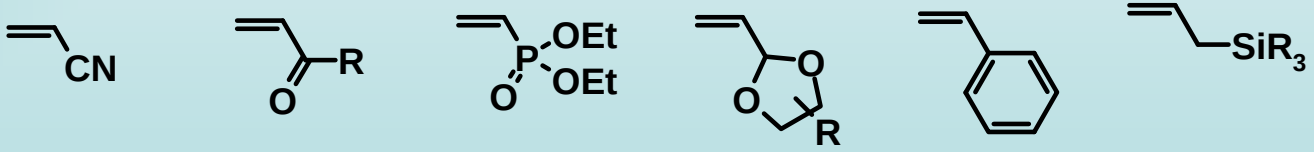
R Maifeld, S.V.; Lee, D. *Chem. Eur. J.* 2005, *11*, 6118
R Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* 2007, *63*, 3919.
R Mori, M. Adv. Synth. Catal. 2007, 349, 121. (in fact entire issue is on metathesis)
R Villar, H.; Frings, M.; Bolm, C. *Chemical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

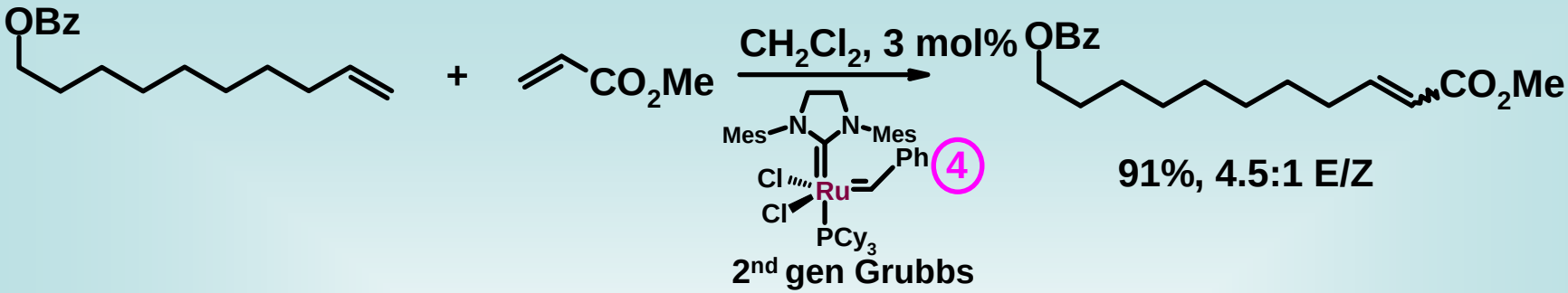


R Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* 2007, *63*, 3919.
R Mori, M. *Adv. Synth. Catal.* 2007, *349*, 121 (entire issue is on metathesis)
R Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* 2007, *36*, 55.
R Maifeld, S. V.; Lee, D. Chem.-Eur.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