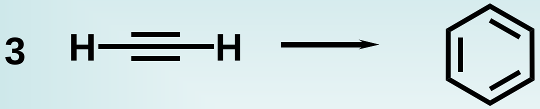
Multistep Reactions

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



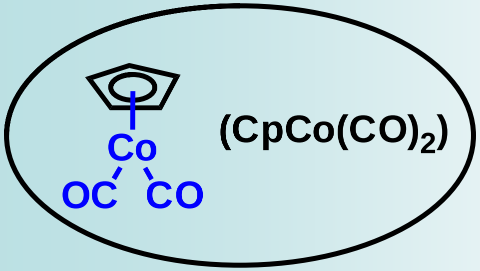
-feasible reaction

-requires 400°; many side reactions

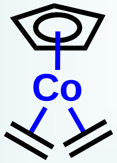
-not synthetically useful as such

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

Co(I) - most common



($CpCo(CO)_2$) ;



($CpCo(ethene)_2$)

Vollhardt, K.P.C.

Rh(I) - almost as common

neutral

$(Ph_3P)_3RhCl$;

Grigg, R.

R Modern Rhodium Catalyzed Reactions Ch 7.3.1

cationic

$[Rh(cod)_2]^+ BF_4^-$

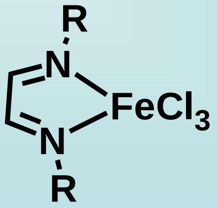
+ diphosphine (i.e., H_8-BINAP)

R Tanaka, K. *Synthesis* 2012, *44*, 323

$[Ir(cod)Cl]_2$ + diphosphine

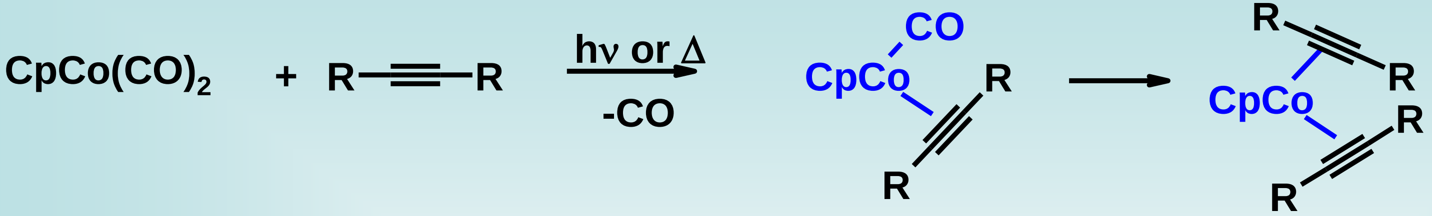
Cp*Ru(cod)Cl

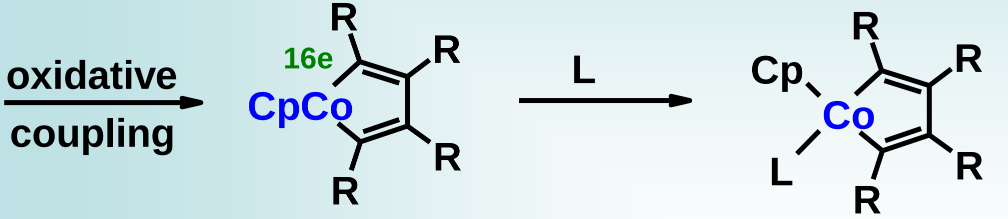
$Ni(cod)_2$ + ligand



+ EtMgBr

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

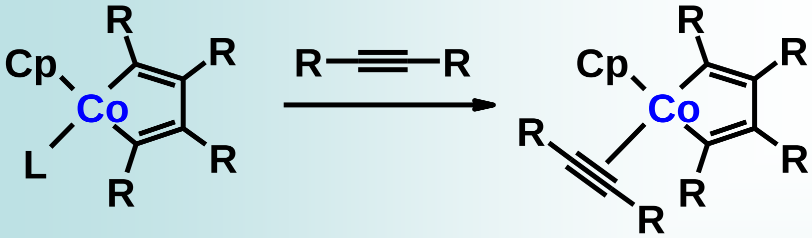




L = solvent in many cases
L = PPh_3 isolated often by Yamazaki group

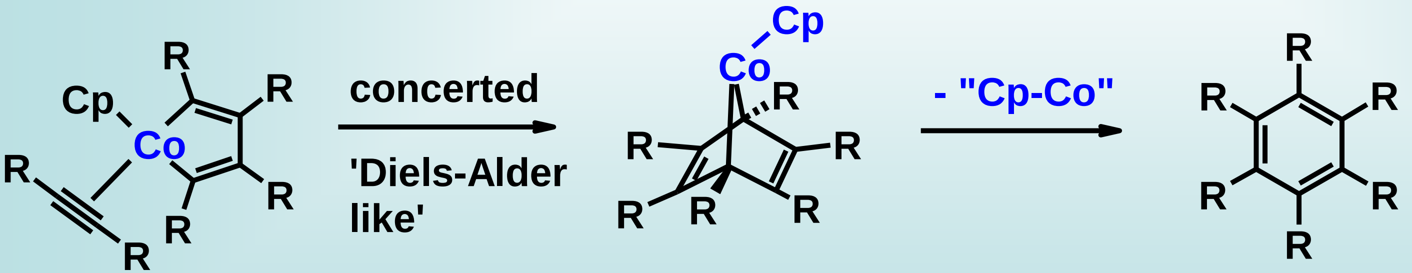
(*Tetrahedron Lett.* 1974, 4549; *J. Organomet. Chem.* 1977, *139*, 157; *J. Am. Chem. Soc.* 1983, *105*, 1907.)

-then



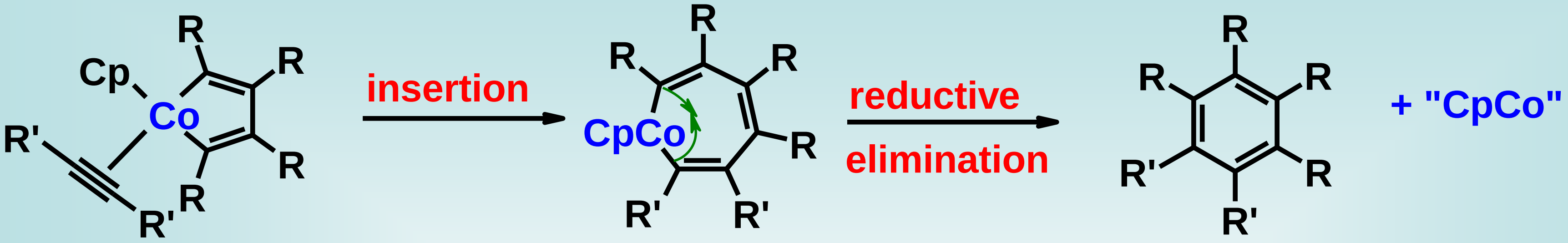
now comes uncertainty.......
-the next step is undecided between two possibilities

Possibility #1 - concerted cycloaddition



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

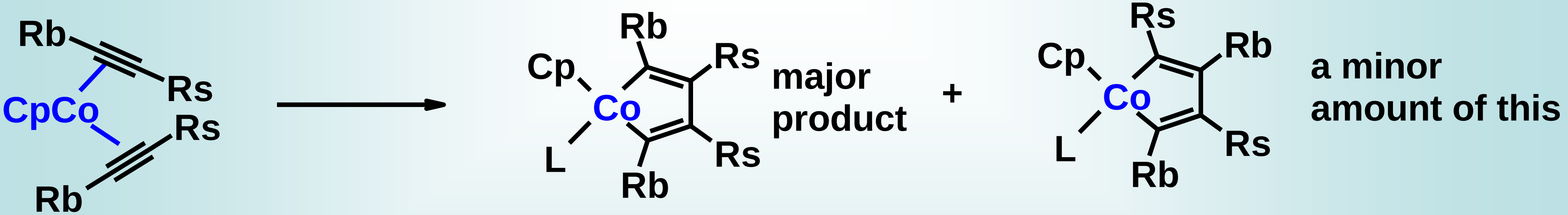
Possibility #2 - Alkyne insertion/reductive elimination



Personal opinion - there are instances where the concerted cycloaddition mechanism is operating
- **more often**, it is the insertion/elimination mechanism that is operating

Regiochemistry

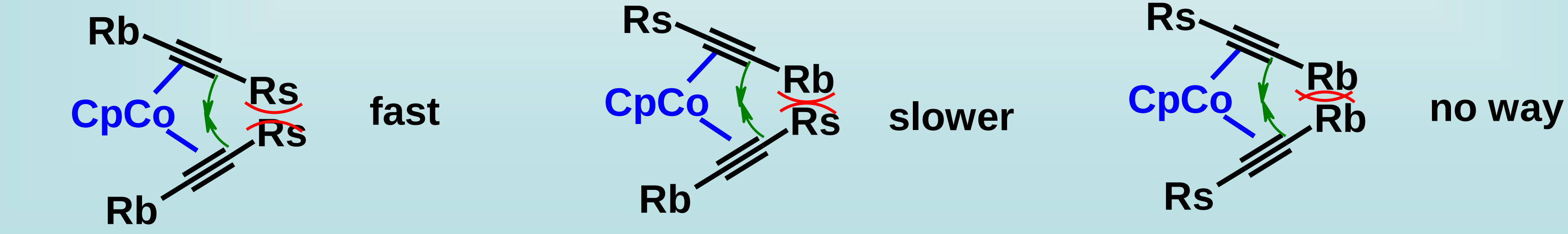
-if one has R(big)≡R(small) , what happens?



major product

a minor amount of this

-simply from sterics

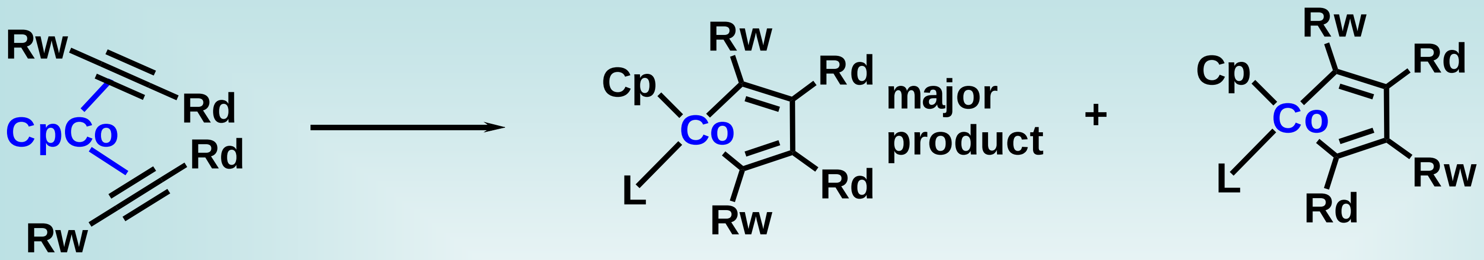


fast

slower

no way

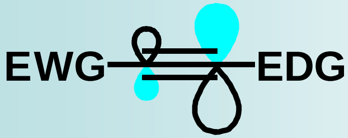
-if one has $R(EDG){-}{\equiv}{-}R(EWG)$, what happens?



major product

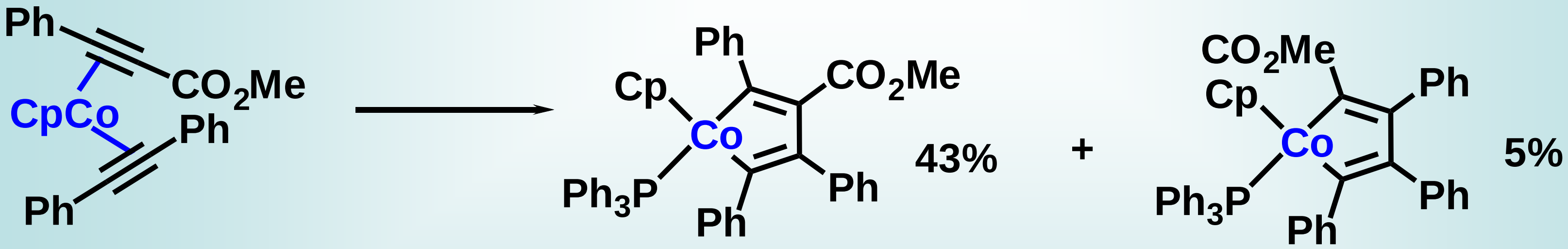
a minor amount of this

-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

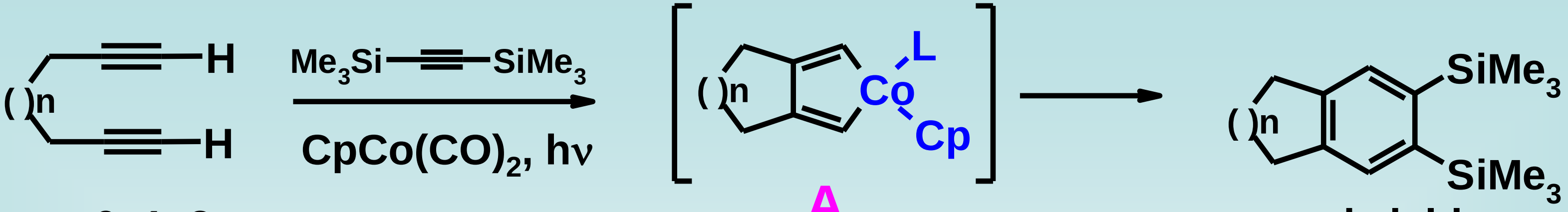
-if sterics and electronic effects compete, the <u>steric</u> effect overwhelm



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

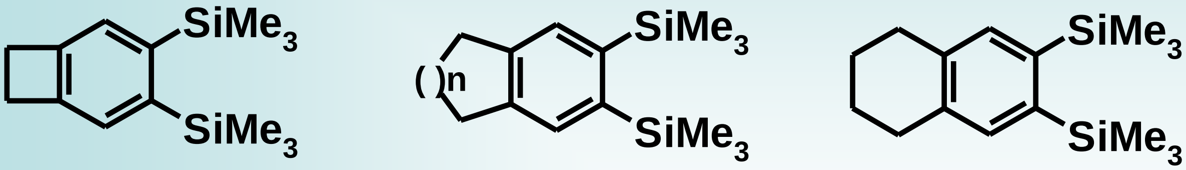
-reaction becomes synthetically useful when BTMSA $Me_3Si{-}{\equiv}{-}SiMe_3$ is used as the third alkyne, as it only reacts with itself very slowly

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

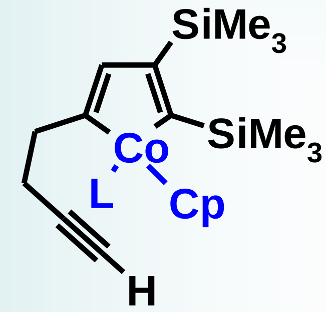


n = 0, 1, 2

good yields

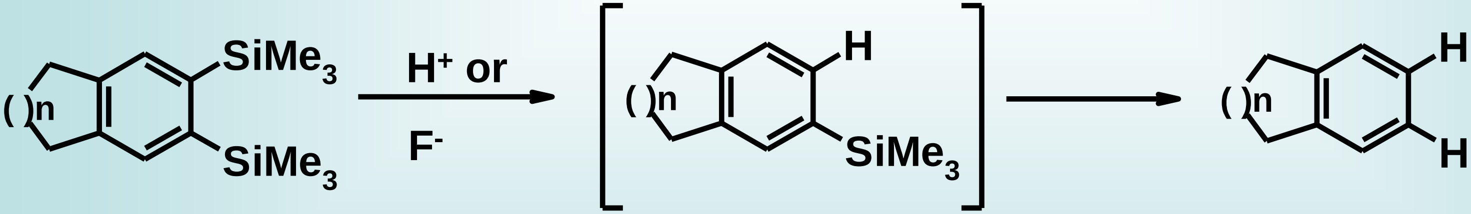


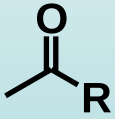
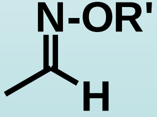
Note; in this case,
the rxn goes through



instead of A

-fortunately, silyl groups are removable from arenes

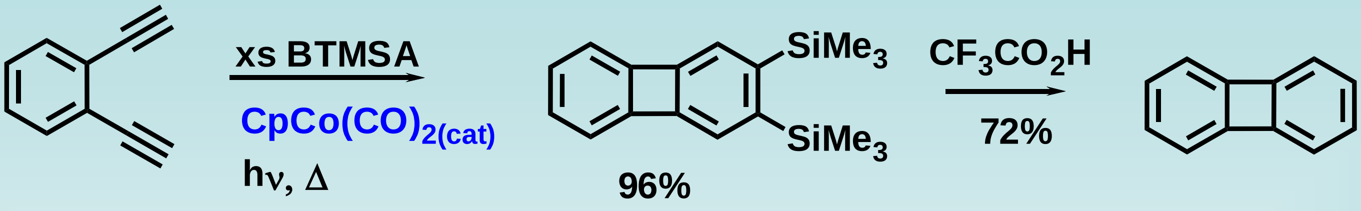


-reactions tolerate a pretty good range of substituents, such as... $-CO_2R$, $-CH_2OH$, $-CH_2OR'$, $-NR'_2$, $-SR'$,  , 

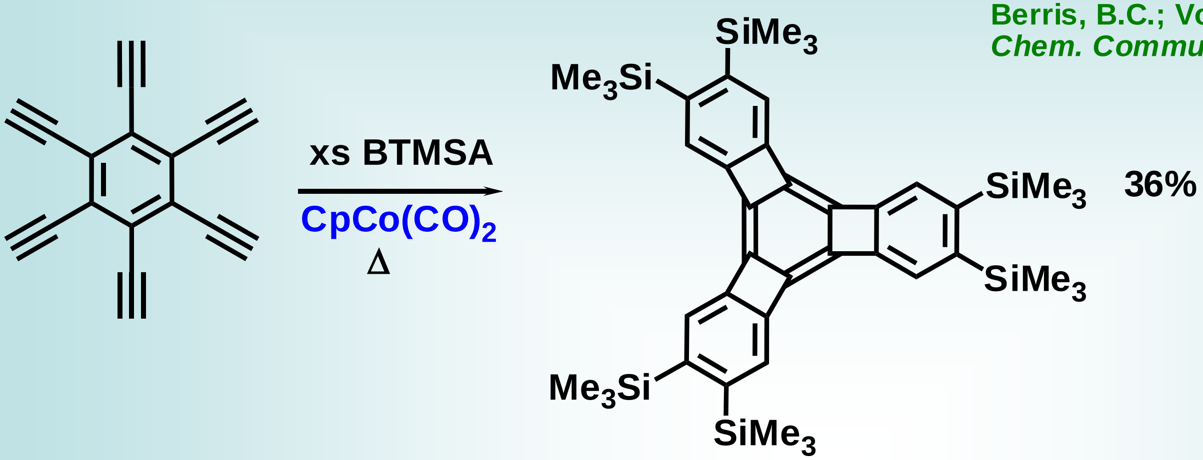
-reaction may be carried out thermally or photochemically (or both)

-reaction is often (but not always) catalytic in cobalt

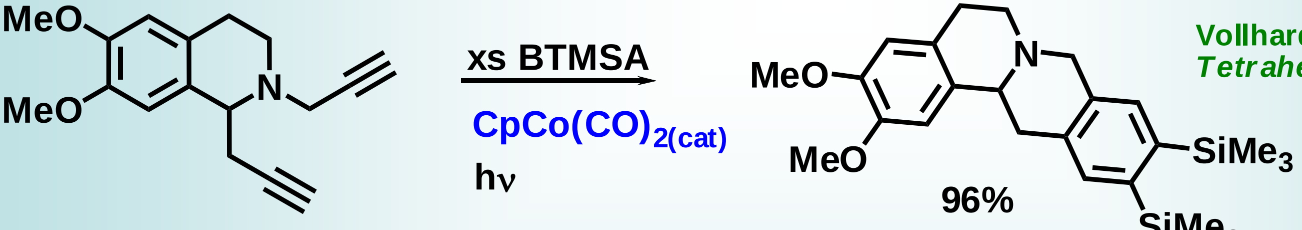
examples



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.

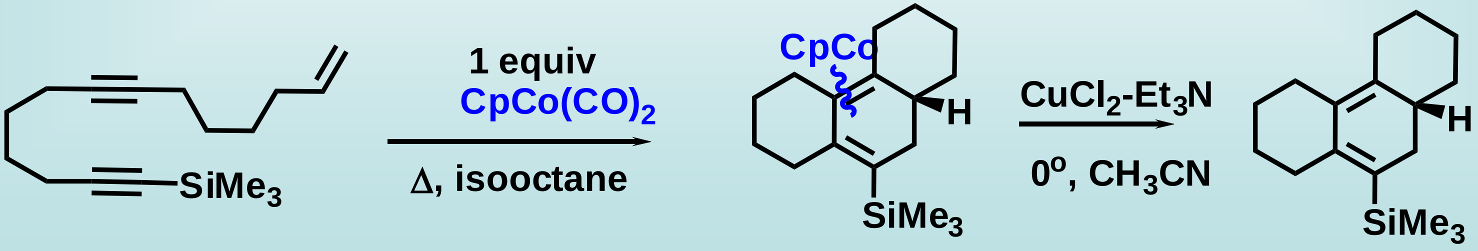


Vollhardt, K.P.C. et al *Tetrahedron* 1983, *39*, 905.

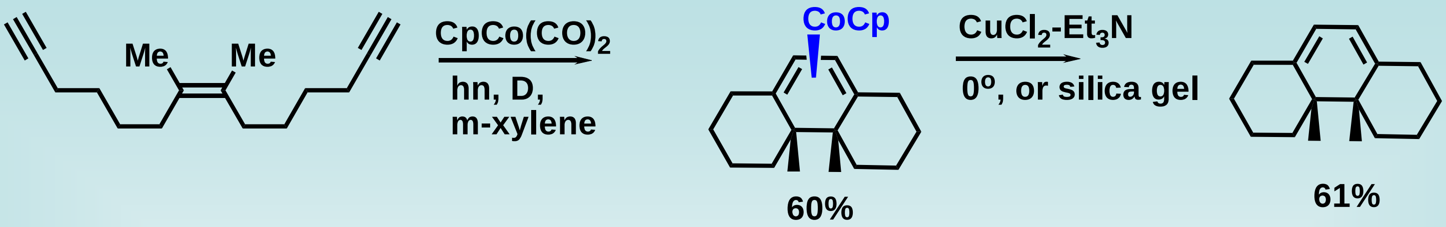
Other cyclization partners

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

-but, the reaction is now almost always stoichiometric in cobalt



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

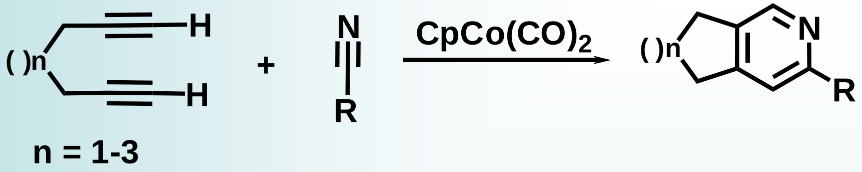


Vollahrdt, K.P.C. et al *J. Org. Chem.* 1984, *49*, 5010; *Angew. Chem. Int. Ed. Engl.* 1981, *20*, 802.

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

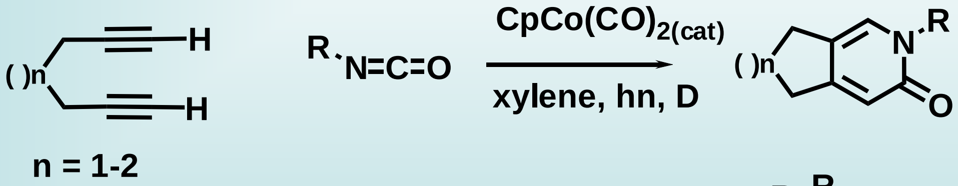
Rhodium (I) complexes *can* be catalytic with alkenes. Can be neutral alkene complexes or cationic ones - please see additinal page on Rh catalysis

-the 'third' partner can also be a nitrile

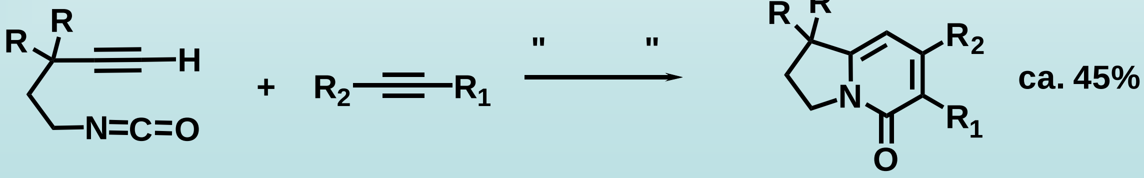


Vollhardt, K.P.C. et al *Tetrahedron* 1983, *39*, 905.

-or an isocyanate



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

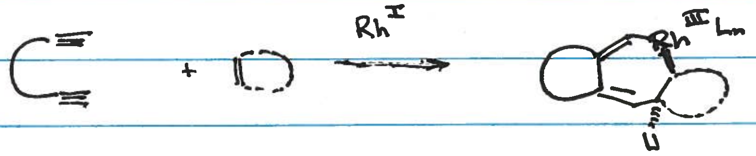


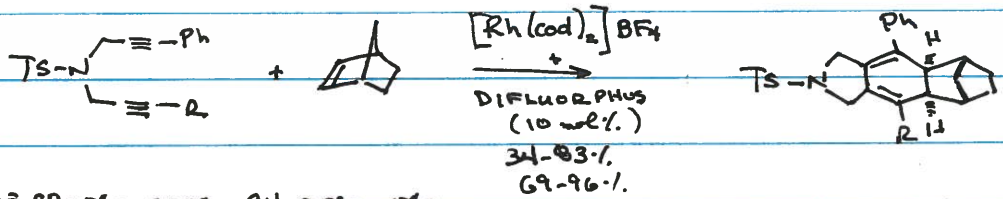
2+2+2 OF TWO ALKYNES & 1 ALKENE.

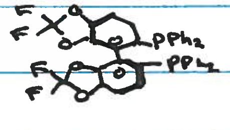
THE STOICHIOMETRIC ORGANOMETALLIC REQUIREMENT IS NOT A NECESSITY FOR OTHER ~~B~~ SPECIES I.E. Rh^{I} - IT WILL OFTEN CYCLO ADD THESE CATALYTICALLY

- THESE ARE OFTEN DONE WITH CYCLIC ALKENES TO MINIMIZE ANY β-HYDRIDE ELIMINATION ISSUES, BUT NOT ALWAYS.

I.E.

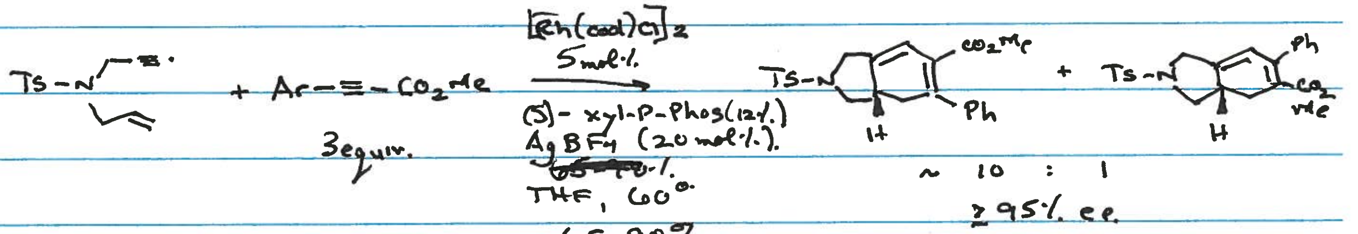


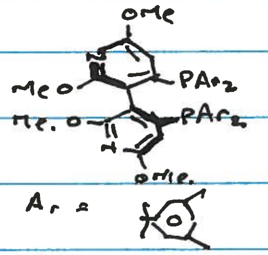




(S) - DIFLUORPHOS

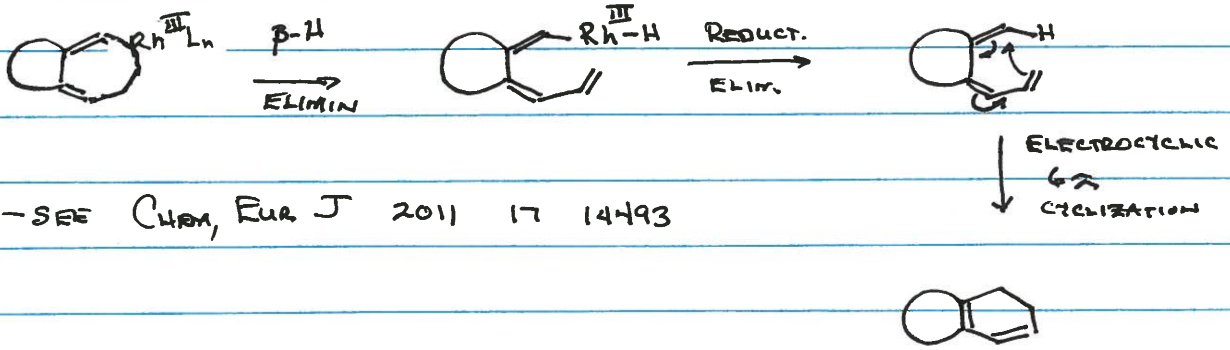
R = CO_2Me, COMe, CH_2OMe, Me





EVANS, P.A. J.Am.Chem.Soc. 2005, 127, 12466.

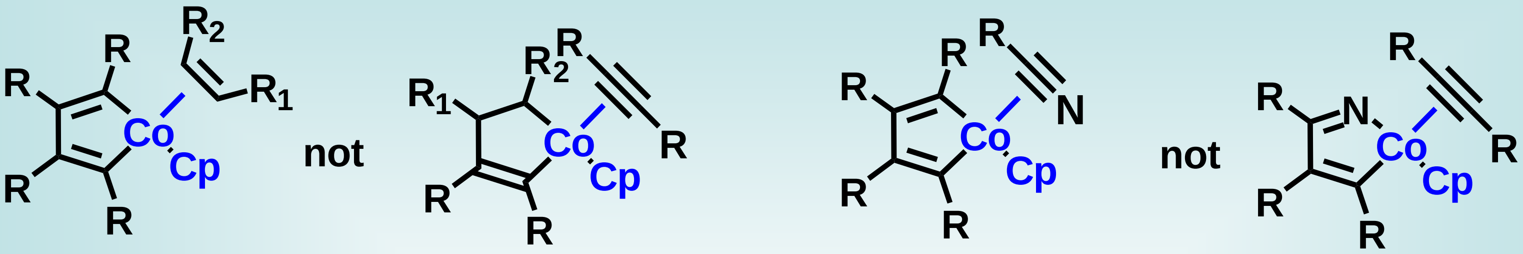
NOTE: EVEN IF β-H ELIMINATION OCCURS, ONE CAN STILL GET CYCLOHEXADIENE - ALKENE REGIOCHEM. WILL BE SUSPICIOUS.



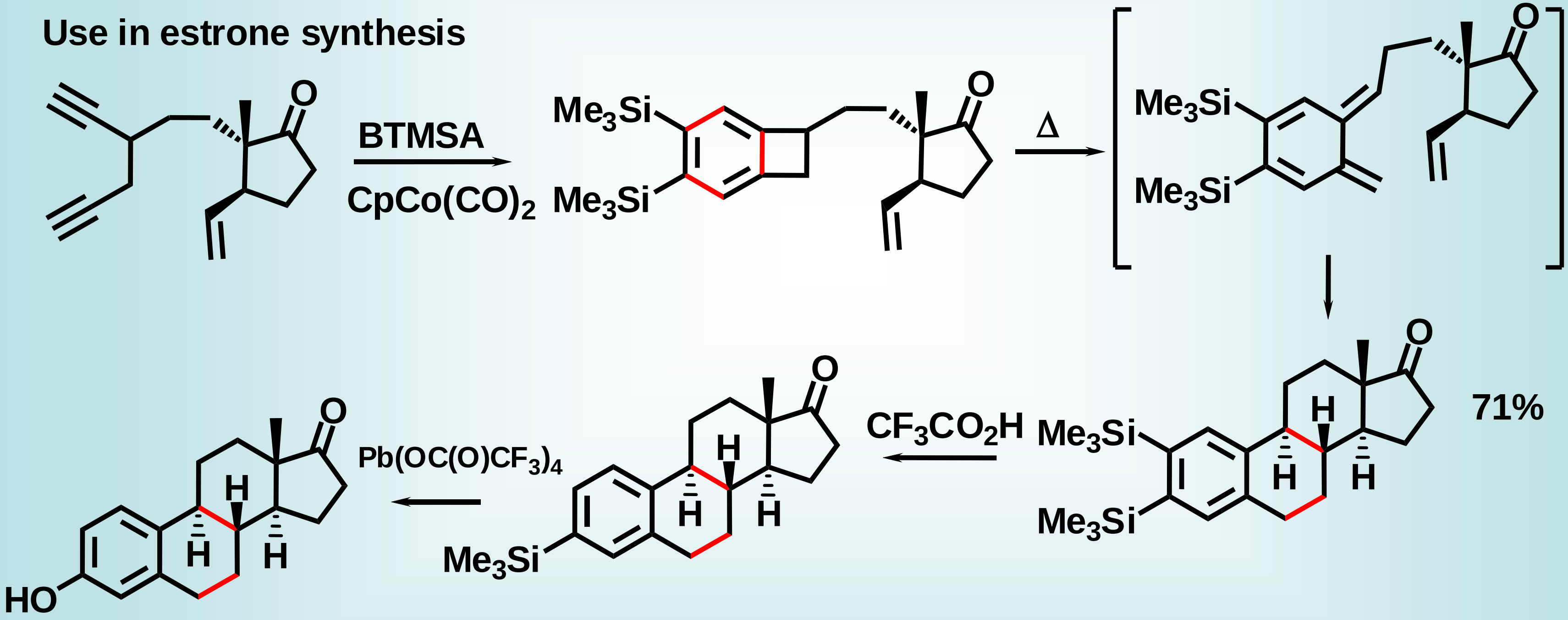
- SEE Chem. Eur. J 2011 17 14493

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

i.e.



Use in estrone synthesis



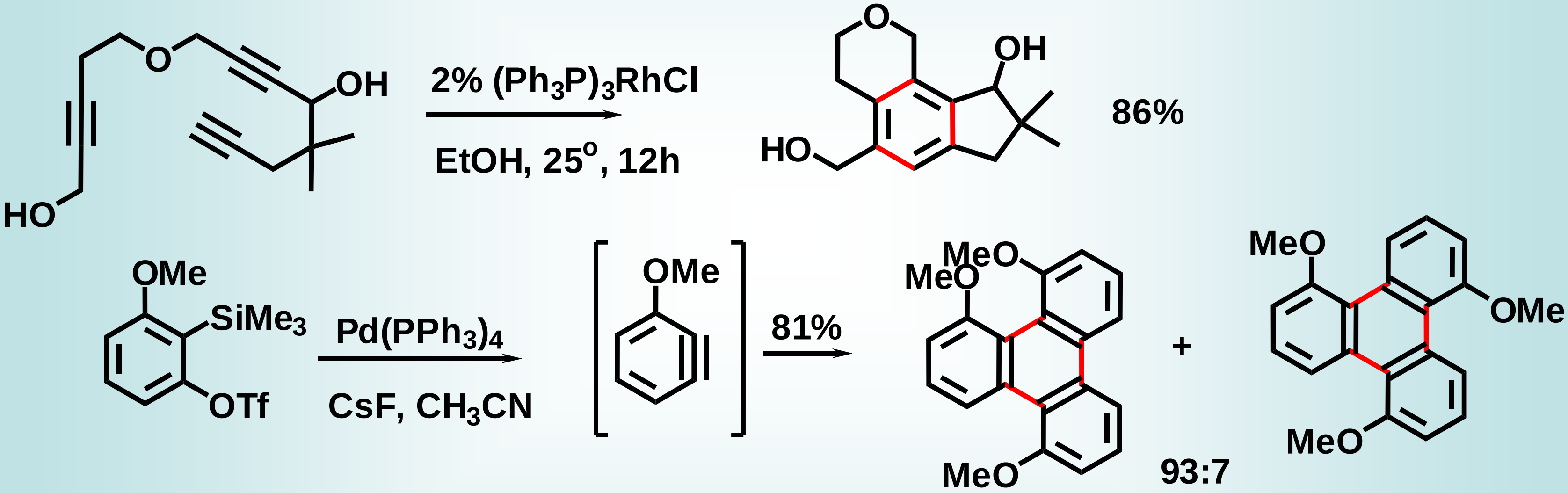
estrone

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

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



Many, many reviews on this

R Galan, B. R.; Rovis, T. *Angew. Chem. Int. Ed.* 2009, *48*, 2830.(all metals, regioselectivity advances)
R Varela, J. A.; Saa, C. *Synlett* 2008, 2571 (pyridines)
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.