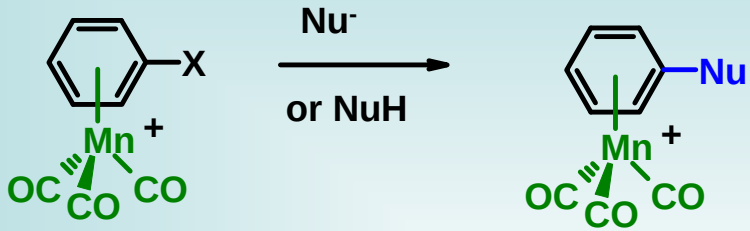
-and if there is a leaving group on the arene, the concept is the same, but the reversible nucleophiles are a different group



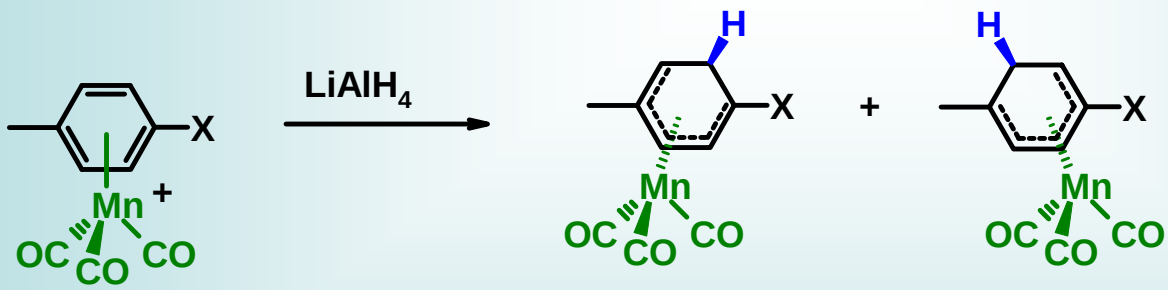
X = Cl, Br, F

-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

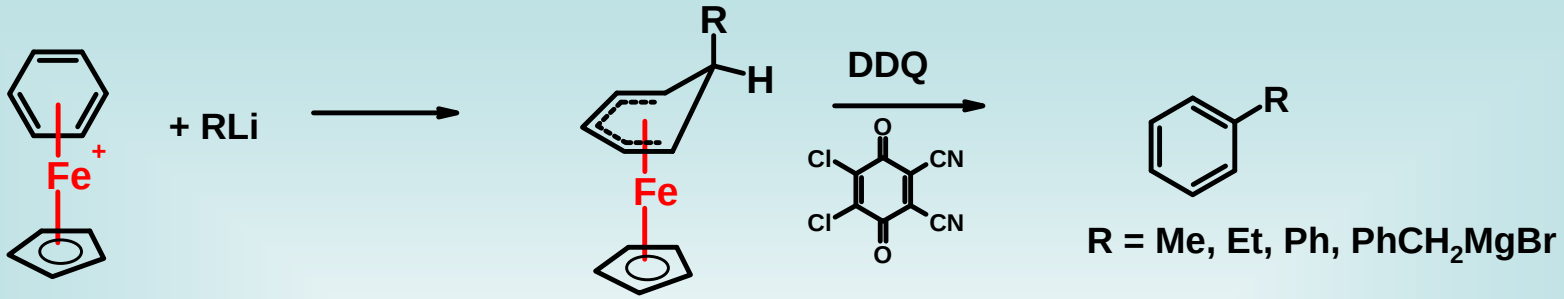


X = Cl 69:37

X = NMe_2 3:97

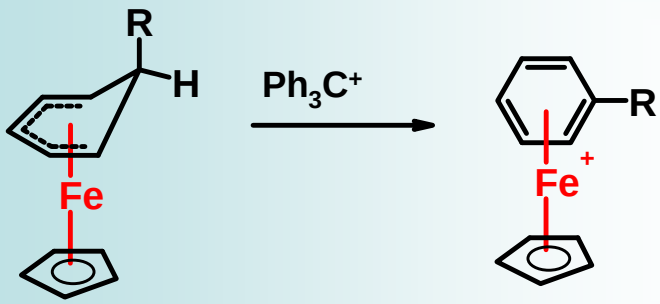
Pauson, P.L. et al *J. Chem. Soc., Dalton Trans.* 1975, 1677 and 1683
Kane-Maguire, L.A.P.; Sweigart, D.A. *Inorg. Chem.* 1979, *48*, 700.
Pearson, A.J. *Tetrahedron* 1992, *48*, 7527
J. Org. Chem. 1991, *56*, 7092.

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

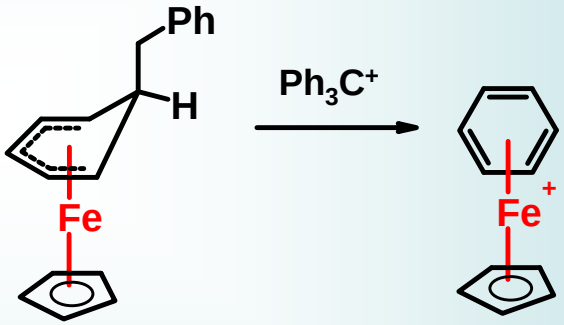


R = Me, Et, Ph, $PhCH_2MgBr$

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



with the exception of benzyl



+ $PhCH_2CPh_3$

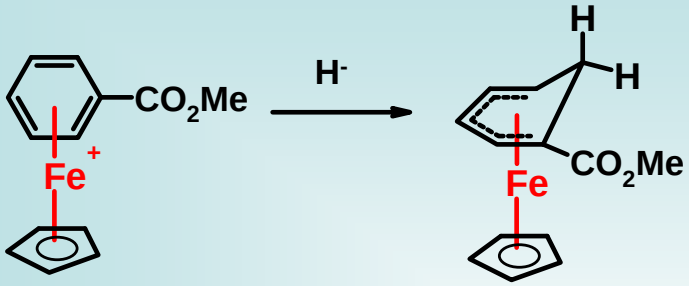
R Astruc, D. *Tetrahedron* 1983, *39*, 4027.
R Adb-El Aziz, A.S.; Bernardin, S. *Chem. Soc. Rev.* 2000, *203*, 219.

A similar reaction pattern for substitutions are observed with the haloarenes

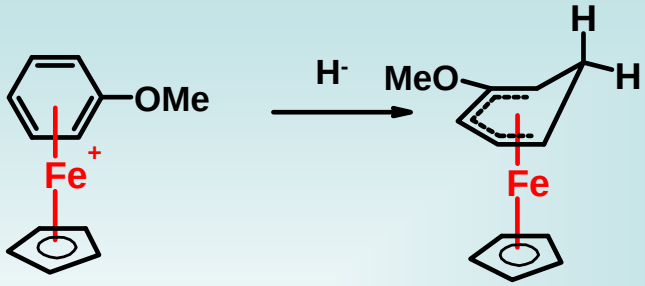
Nu^- = PhO^-, RO^-, RS^-, R_2NH, $NaCH(EWG)_2$

-fairly analogous trend is seen in the kinetic regiochemistry

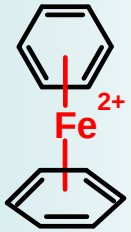
EWG - ortho attack



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.

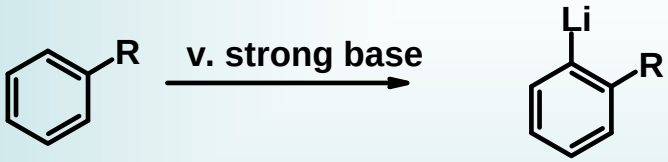
Reactions on  are very similar

-see Astruc review if interested

Effect #2 of electron withdrawing effect of arene-Cr(CO)$_3$

-enahanced acidity of arene ring protons

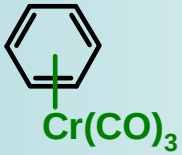
Consider



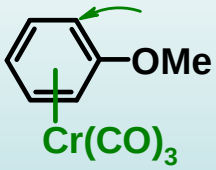
reaction is feasible, but.....pK$_a$'s are 38-42

the pK$_a$'s of arene-Cr(CO)$_3$ are

6-7 pK$_a$ units more acidic



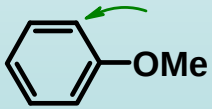
pK$_a$ = 34.8



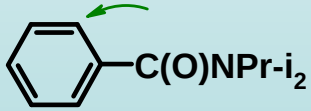
pK$_a$ = 33.0

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

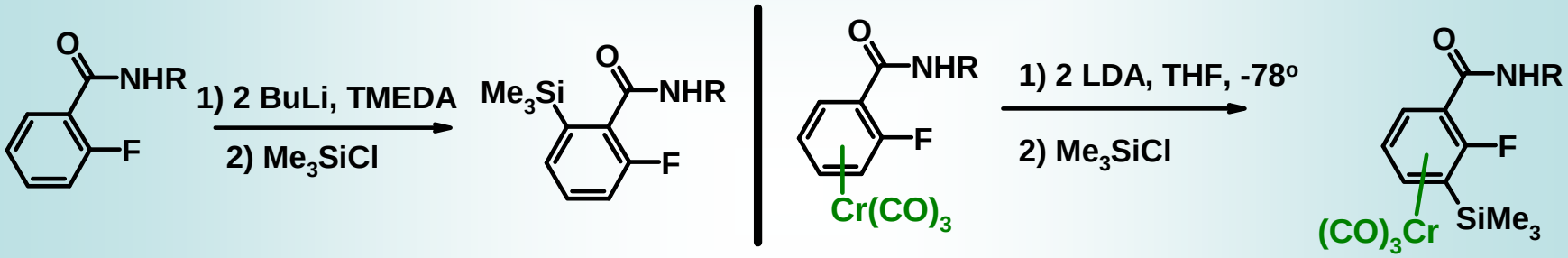
-excellent for *ortho*- functionalization of aromatics; and

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

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

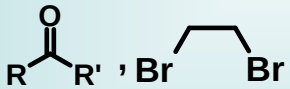
for Cr complexes $-F > -C(O)NHR > -CH_2NR_2 = -OMe >> -CH_2OMe > -NR_2, -SR$

So

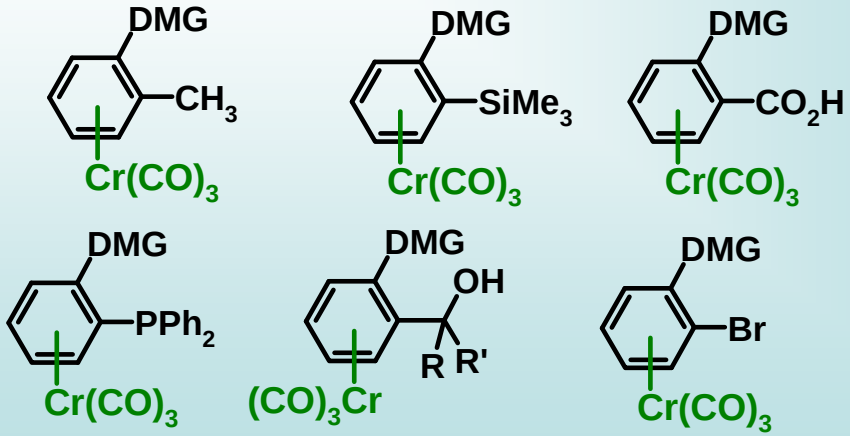


can be trapped by a wide range of E^+

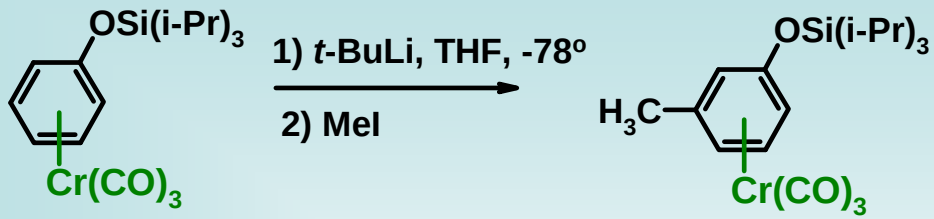
CH_3I, Me_3SiCl, CO_2, Ph_2PCl,



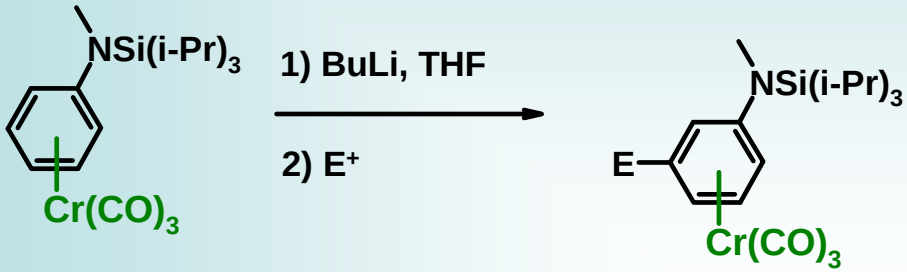
to give



further



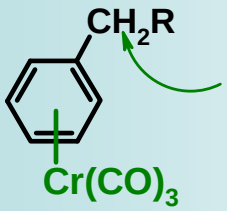
this meta metallation is unheard of in chemistry of free arenes



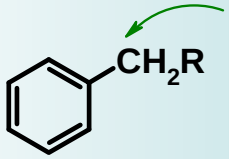
Widdowson, D.A. *J. Chem. Soc., Chem. Commun.* 1983, 955.
Fukui, M., et al *Tetrahedron Lett.* 1982, *23*, 1605.

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

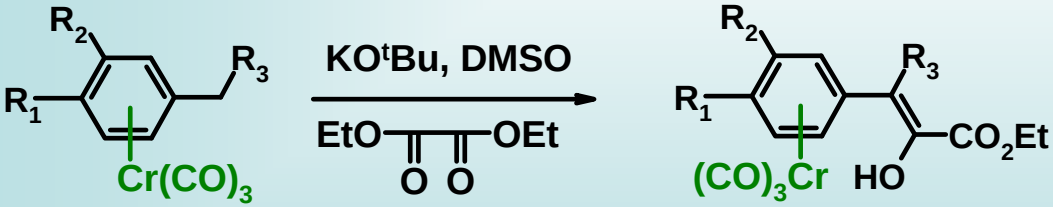


pK_a ca. 40

-so benzylic deprotonation is quite easy

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

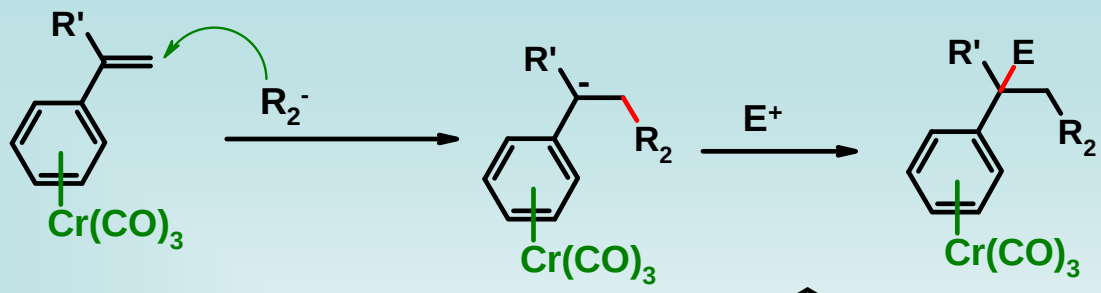
-as a result, one can often do benzylic deprotonation reactions which fail with the free arene

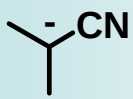
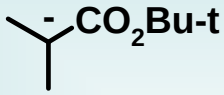
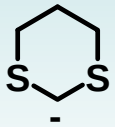


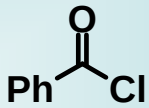
Jaouen, G. et al

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, 

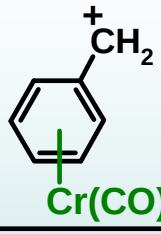
Semmelhack, M. F. Seufert, W.; Keller, L. *J. Am. Chem. Soc.* 1980, *102*, 6586.
Uemura, M.;Minami, T.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* 1984, 1193.

-appears to be both a kinetic and a thermodynamic effect

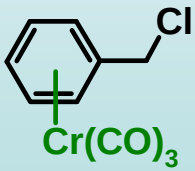
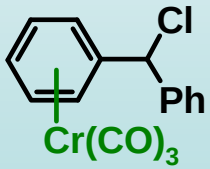
R Davies, S. G. et al *Adv. Met. Org. Chem.* 1991, *2*, 1.

Effect #4 Stabilization of Benzylic Cations

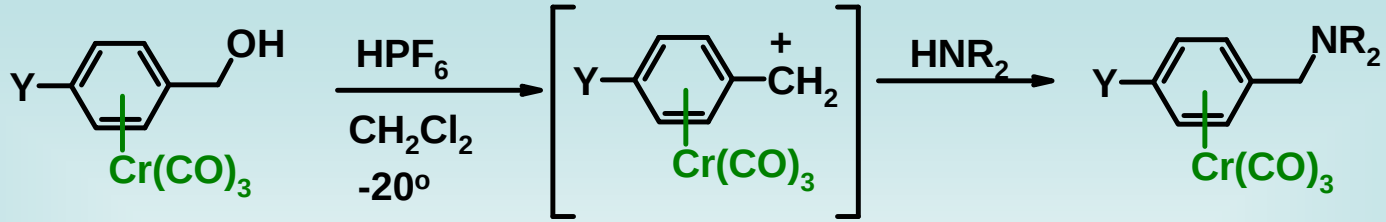
-recall our discussion of pK_{R+} values....

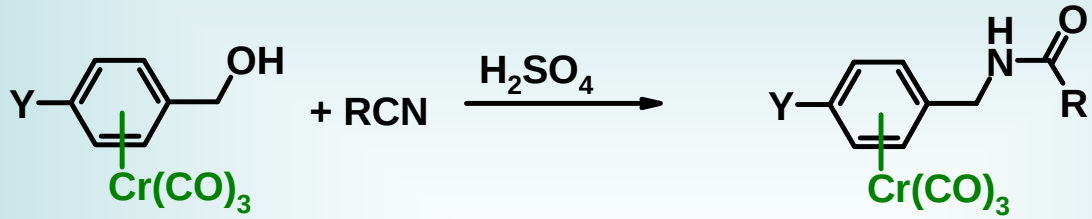
$PhCH_2^+$ < -17.3 Ph_2CH^+ -13.4  -11.8 Ph_3C^+ -6.6

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



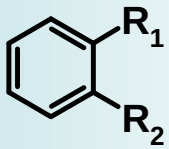


-this Ritter reaction only works with 3° benzylic halides

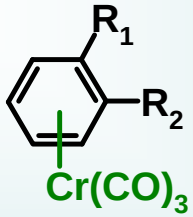
R Davies, S.G. *Synlett* 1993, 323.

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

-stereochemistry



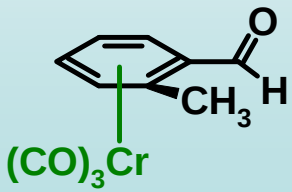
is flat, achiral
σ- plane of symmetry



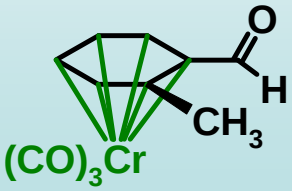
σ- plane is gone
Chiral

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

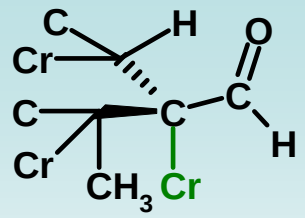
Consider

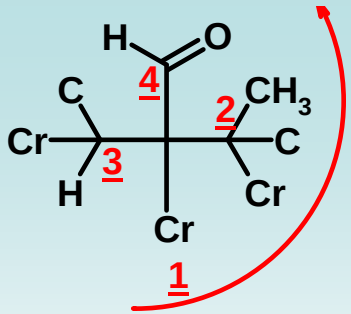


≡



-at position 1 we have

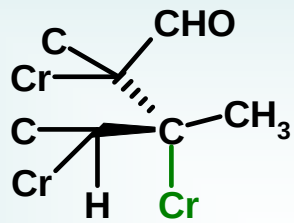


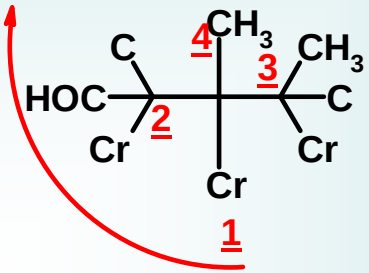


counterclockwise

-therefore, (S)-enantiomer

-at position 2 we have





clockwise

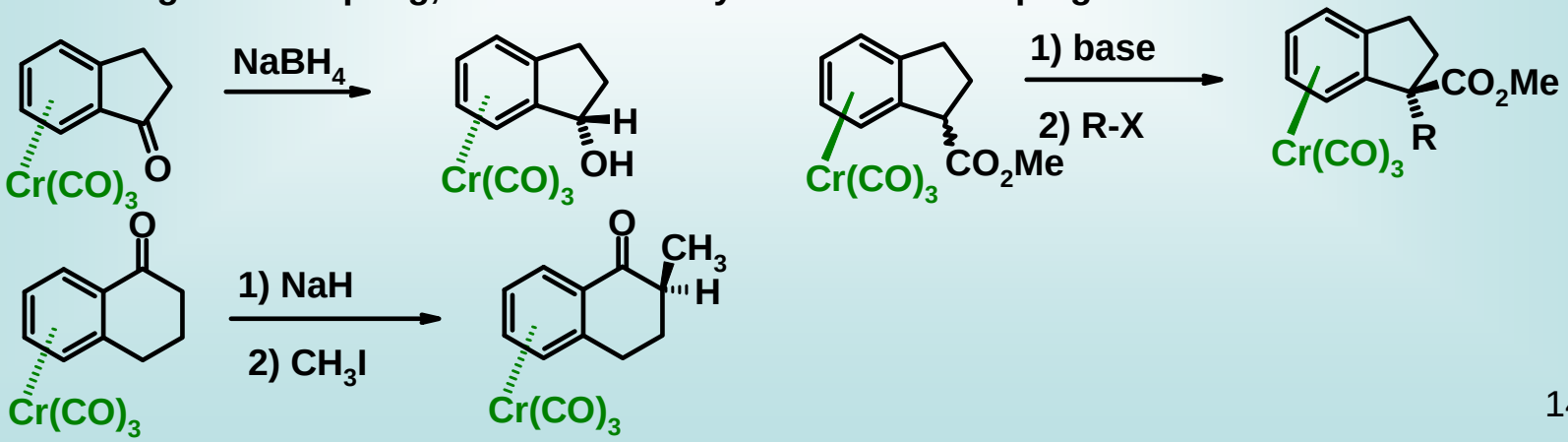
-therfore, (R)-enantiomer

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

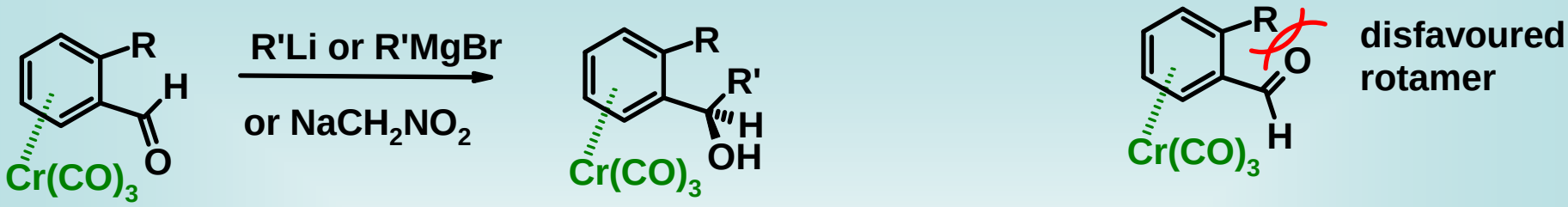
Note: Davies just uses the label at position 1, as the 2-position is then defined automatically

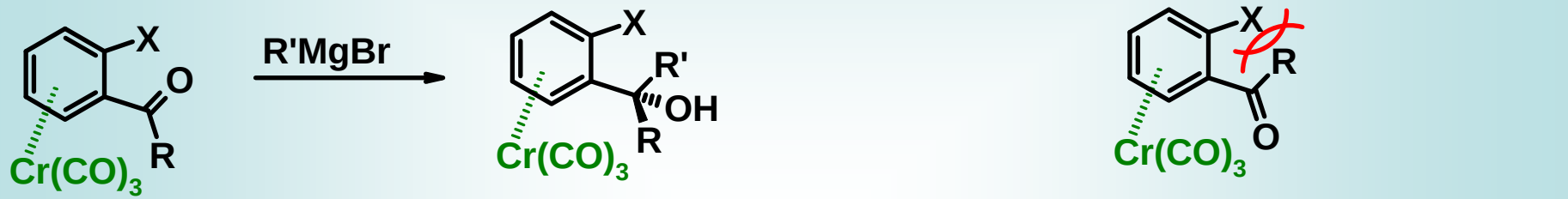
-chiral centre (or plane); therfore should be able to do asymmetric reactions

-will give a sampling, as this is a fairly new and developing area

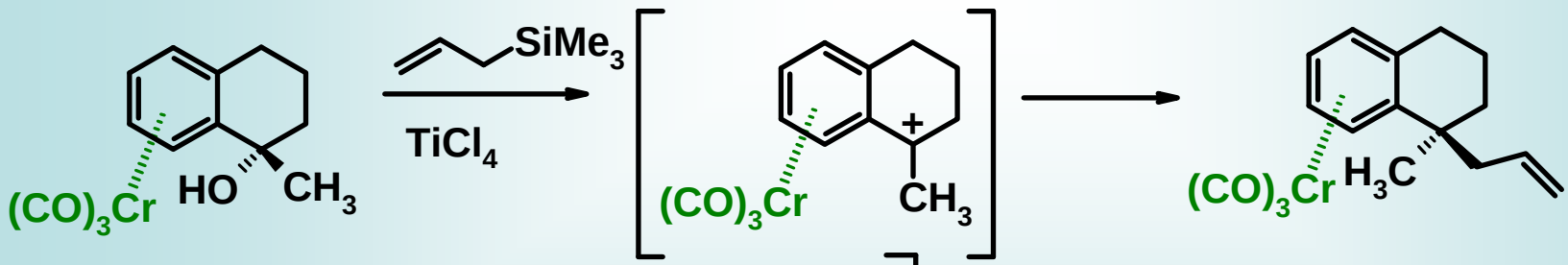


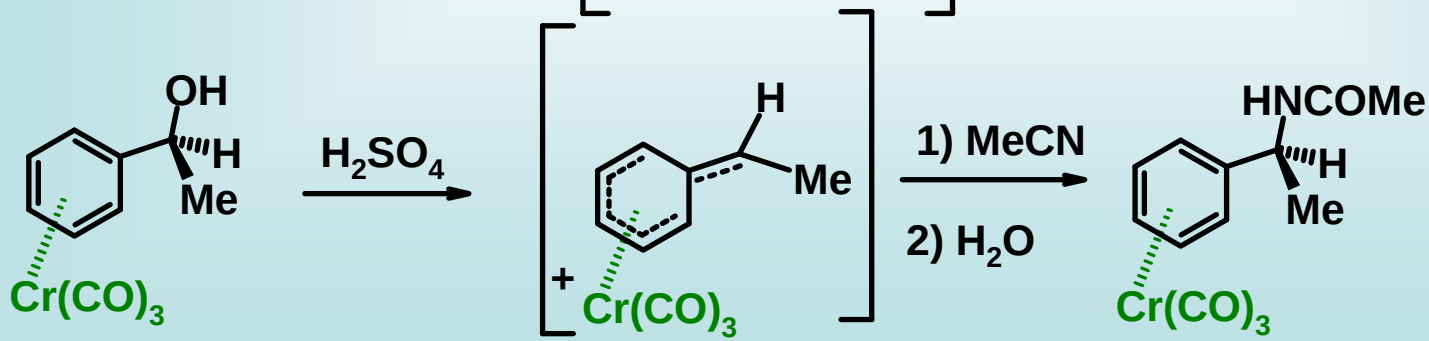
Acyclic cases

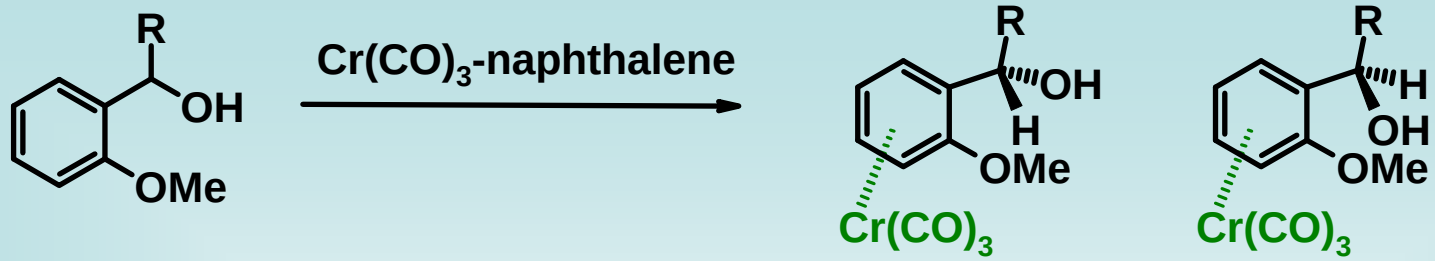




X = CH_3, OR_2 R = Me, Et, alkyl







major

because

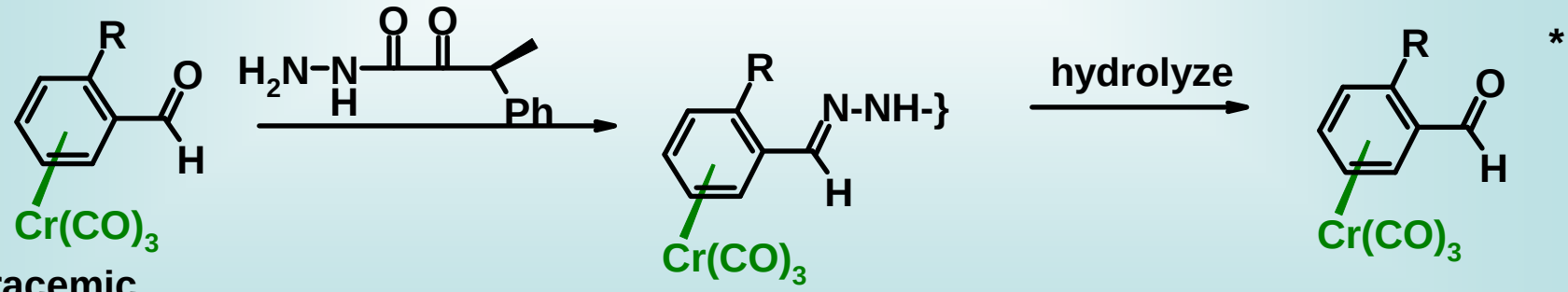
favoured

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)



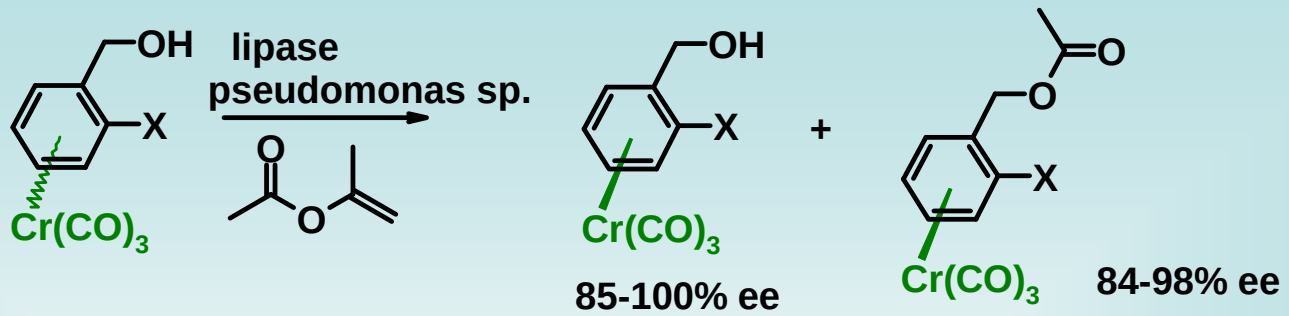
racemic

separate diastereomers

enantomerically pure

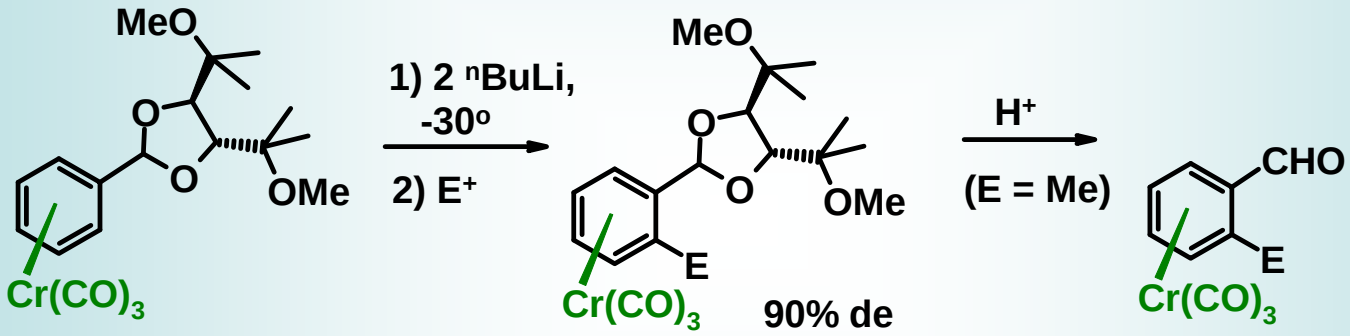
Classical Resolution

2) kinetic resolution



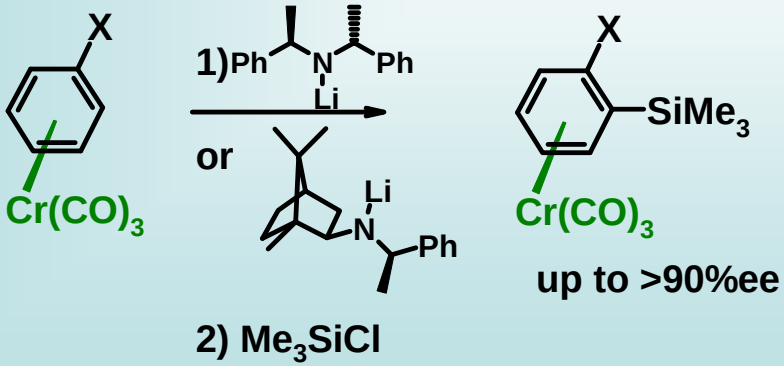
Uemura, M. et al *Tetrahedron Lett.* 1990, *31*, 3603; Jaouen, G. et al *J. Chem. Soc., Chem. Commun.* 1984, 1284.

3) chiral auxiliaries



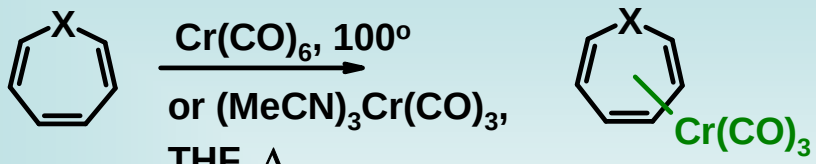
Kondo, Y.; Green, J.R.; Ho, J. *J. Org. Chem.* 1993, *58*, 6182.

4) enantioselective functionalization



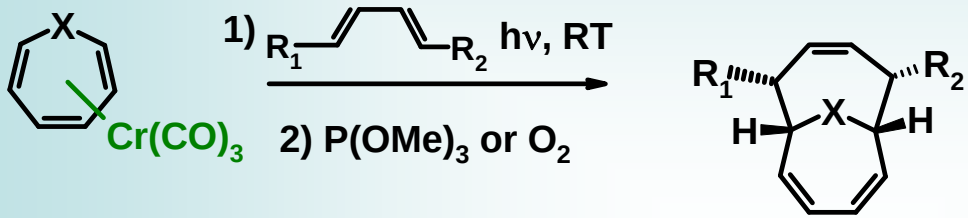
Kundig,E.P. at al *Tetrahedron Lett.* 1994, *35*, 3497
Simpkins, N.S. et al *J. Org. Chem.* 1994, *59*, 1961
Siwek, M.J.; Green, J.R. *J. Chem. Soc., Chem. Commun,* 1996, 2359.

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



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

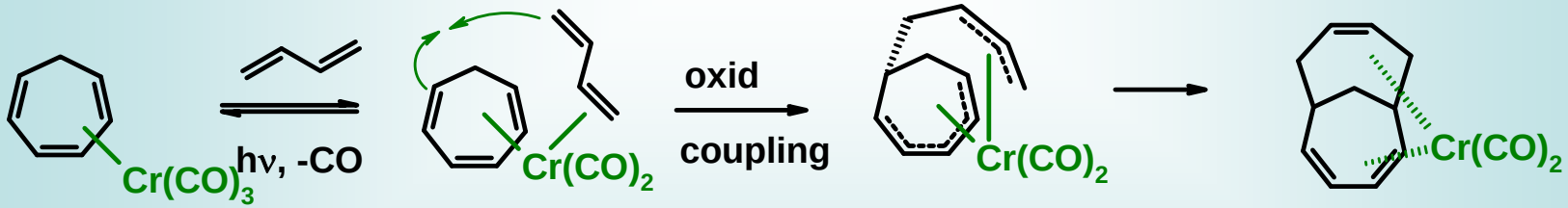
unlike Fe complexes, this is η^6



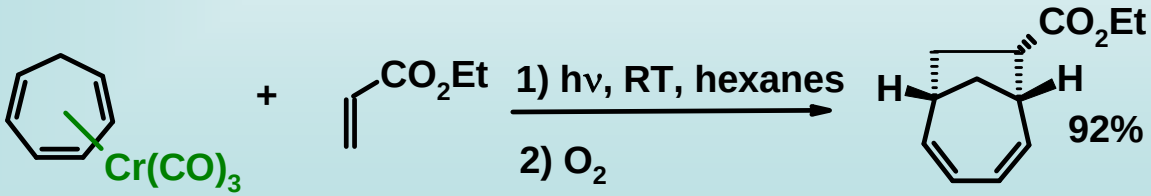
[6+4] cycloaddition
good yields

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

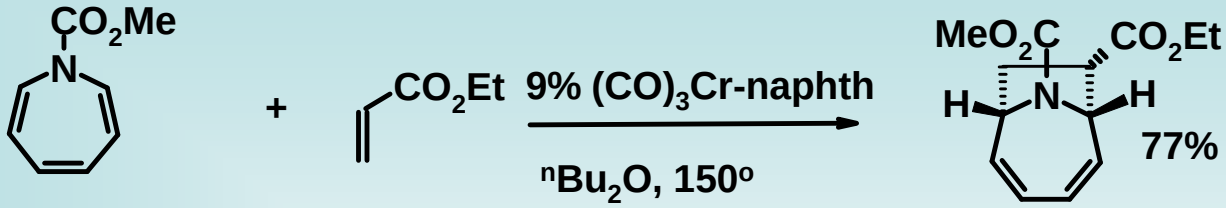


-this is stepwise in nature, so there is no 'concertedness' reason why the [6+2] should fail, so...



92%

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



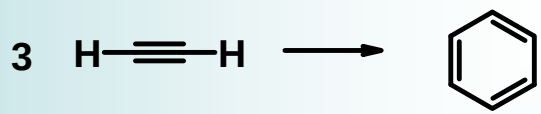
R Rigby, J.H. *Adv. Met-Org. Chem.* 1985, *4*, 89.
R Rigby, J.H. *Tetrahedron* 1999, *55*, 4251.
R Rigby, J.H. *Org. React.* 1997, *49*, 331.

Multistep Reactions

The [2+2+2] Cycloaddition

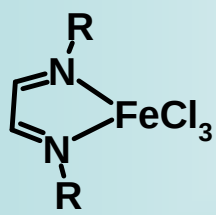
- important method of making six membered rings
-also, many of the other multistep processes are based on this reaction

-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...

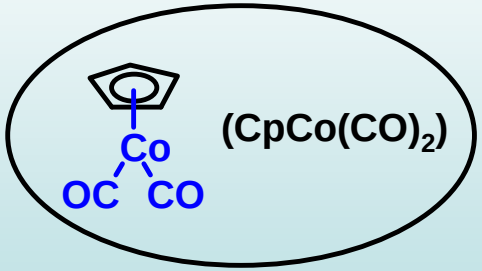


+ EtMgBr ;

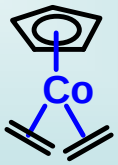
$(Ph_3P)_3RhCl$;

Grigg, R.

R Modern Rhodium Catalyzed Reactions Ch 7.3.1



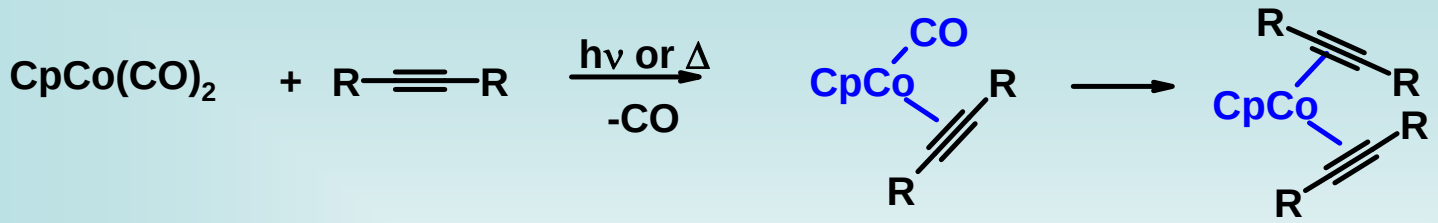
$(CpCo(CO)_2)$;

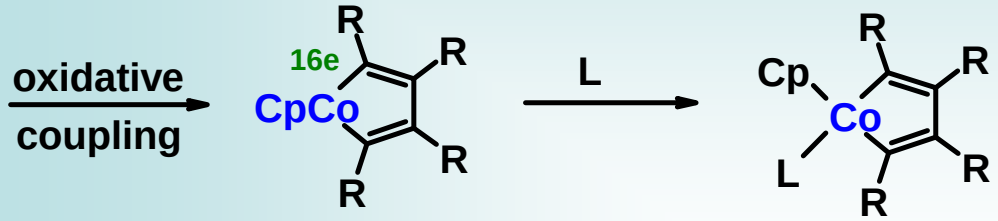


$(CpCo(ethene)_2)$

Vollhardt, K.P.C.

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

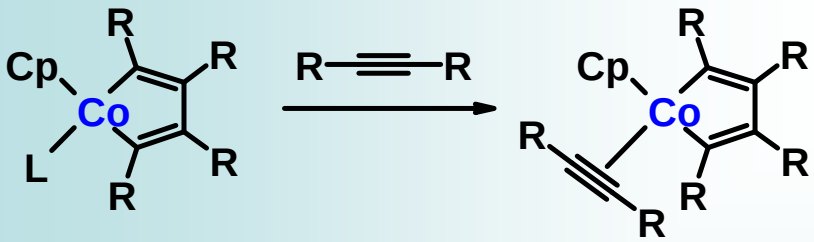




L = solvent in many cases
L = PPh_3 isolated often by Yamazaki group

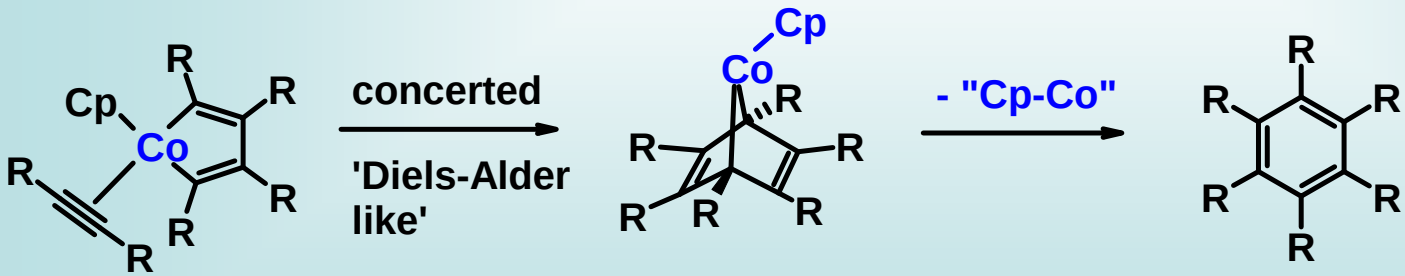
(*Tetrahedron Lett.* 1974, 4549; *J. Organomet. Chem.* 1977, *139*, 157; *J. Am. Chem. Soc.* 1983, *105*, 1907.)

-then



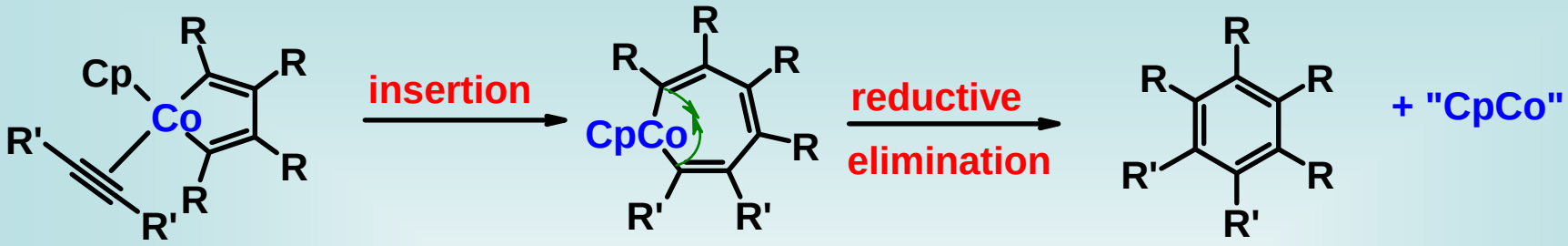
now comes uncertainty.....
-the next step is undecided between two possibilities

Possibility #1 - concerted cycloaddition



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

Possibility #2 - Alkyne insertion/reductive elimination

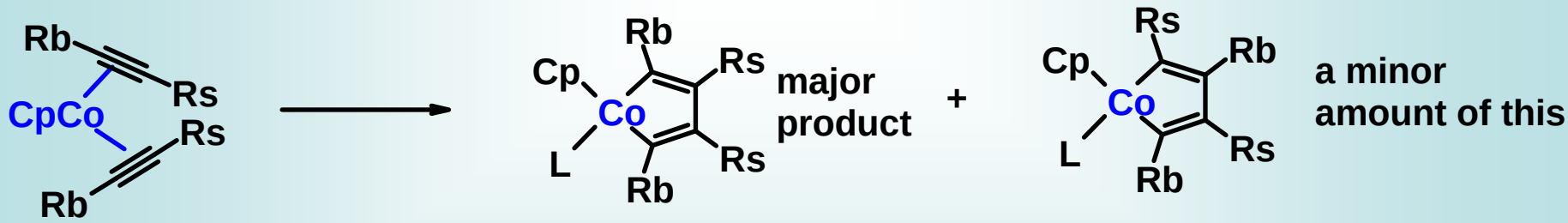


Personal opinion - there are instances where the concerted cycloaddition mechanism is operating

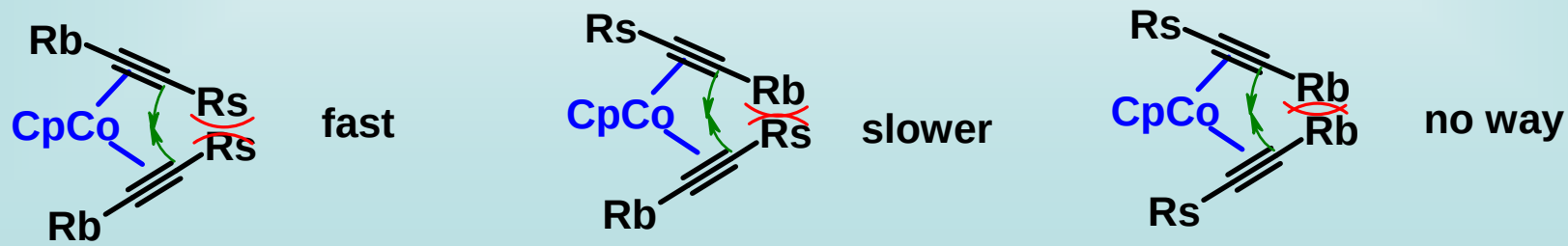
- <u>more often</u>, it is the insertion/elimination mechanism that is operating

Regiochemistry

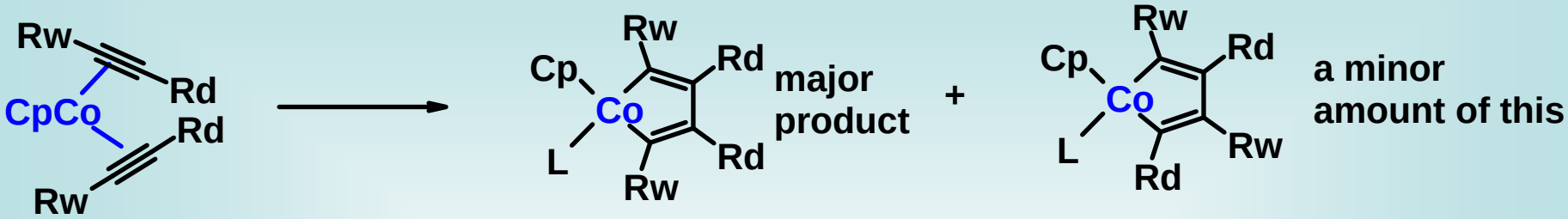
-if one has R(big)—≡—R(small) , what happens?



-simply from sterics

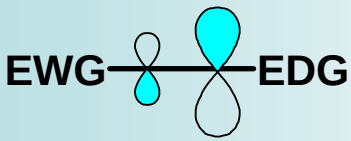


-if one has R(EDG)—≡—R(EWG) , what happens?



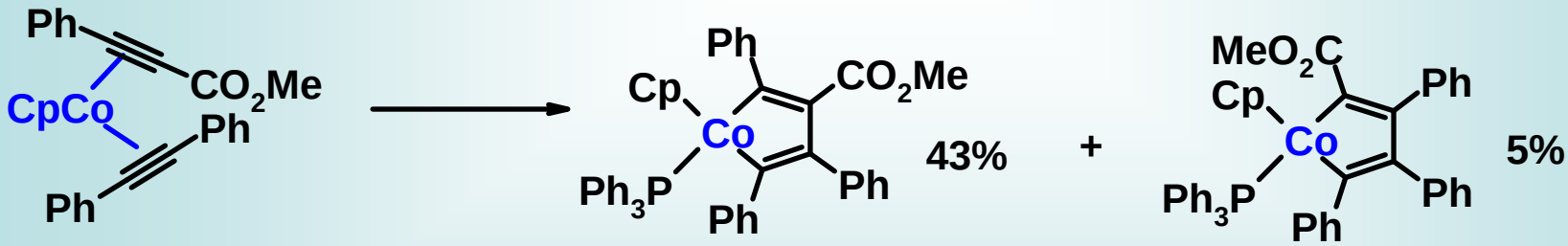
-reason - oxidative coupling step proposed to operate under orbital control

- 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

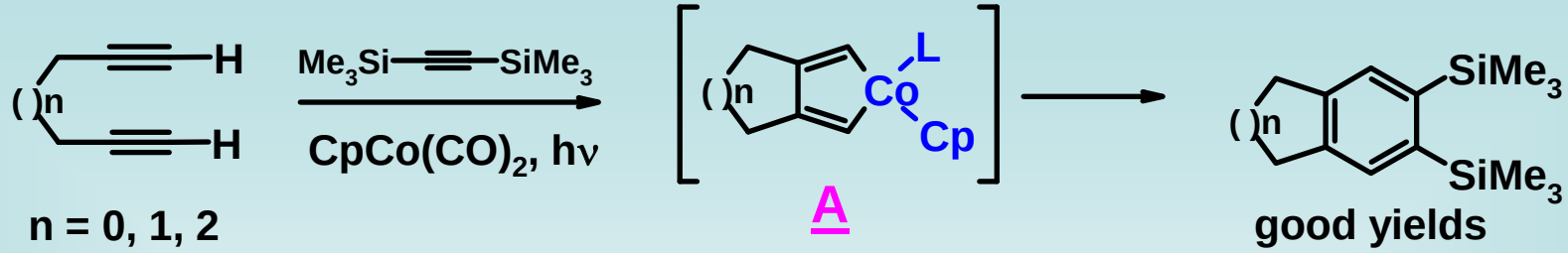


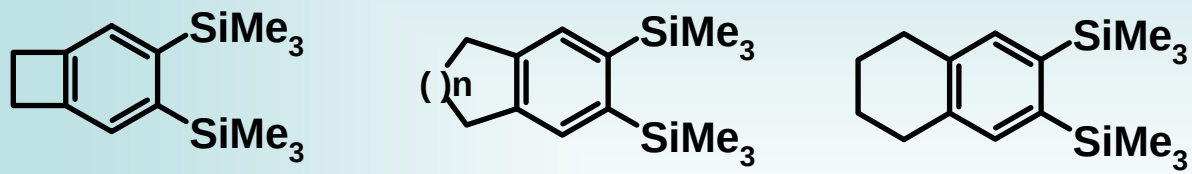
-there is still a third alkyne to participate in 2+2+2, so often one gets further regiochemical mixtures

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

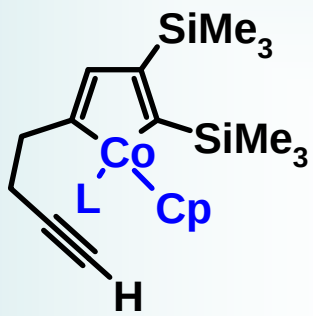
-particularly synthetically useful reaction when the two other alkynes are joined

i.e.,



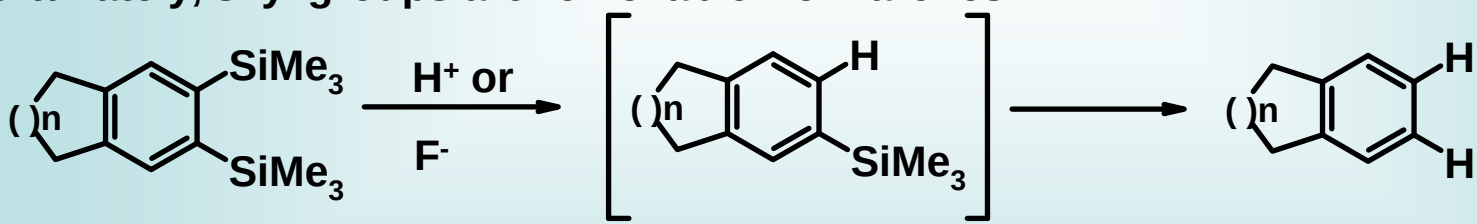


Note; in this case,
the rxn goes through

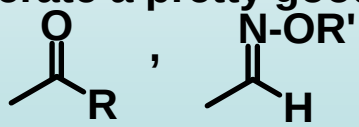


instead of A

-fortunately, silyl groups are removable from arenes

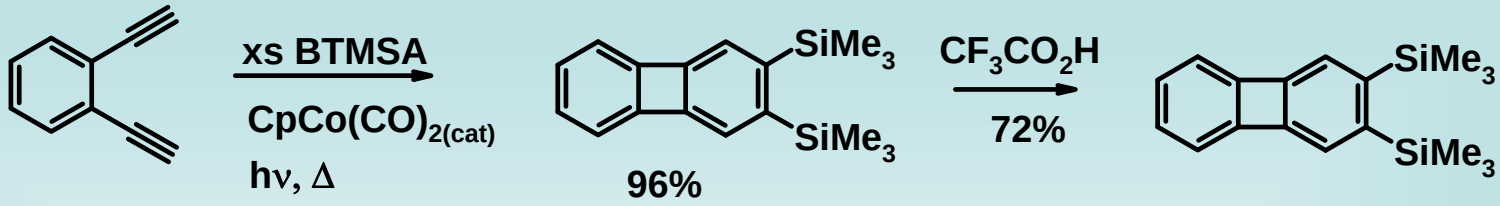


-reactions tolerate a pretty good range of substituents, such as... $-CO_2R$, $-CH_2OH$, $-CH_2OR'$, $-NR'_2$, $-SR'$,

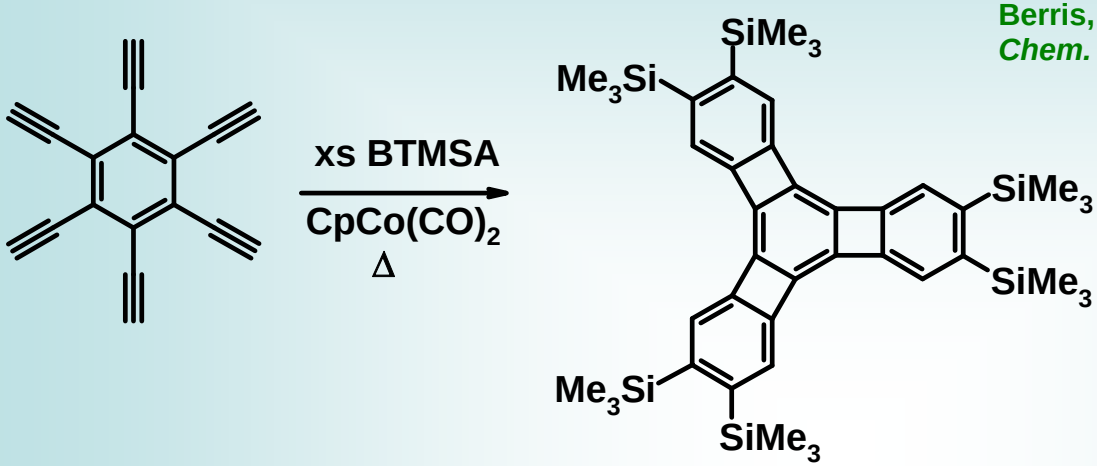


-reaction may be carried out thermally or photochemically (or both)
-reaction is often (but not always) catalytic in cobalt

examples

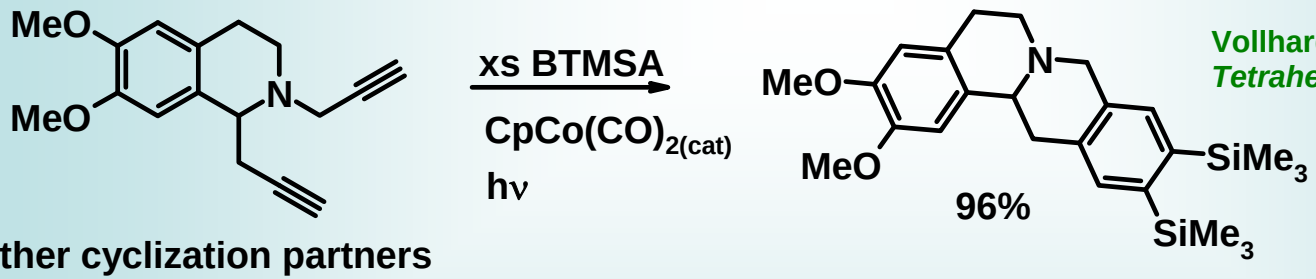


Berris, B.C.; Vollhardt, K.P.C. *J. Chem. Soc., Chem. Commun.* 1982, 953.



36%

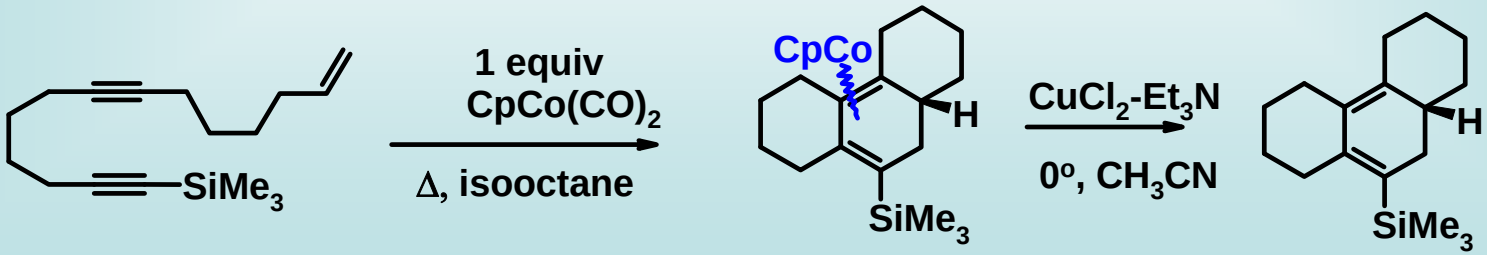
Dierks, R.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* 1983, *39*, 3150.



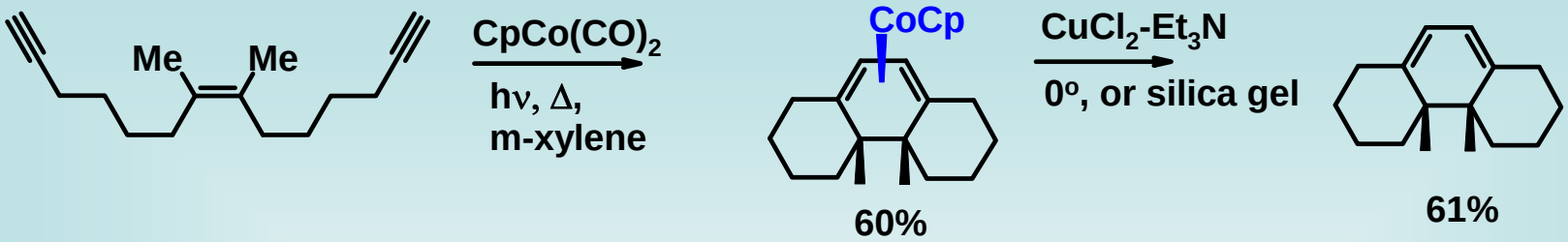
Vollhardt, K.P.C. et al *Tetrahedron* 1983, *39*, 905.

Other cyclization partners

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



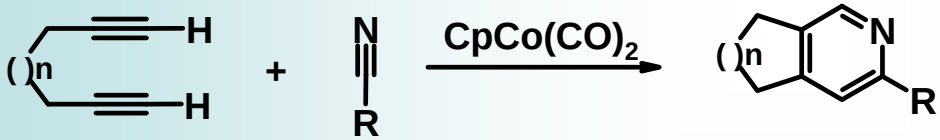
Sternberg, E.D.; Vollhardt, K.P.C. *J. Org. Chem.* 1984, *49*, 1564.



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

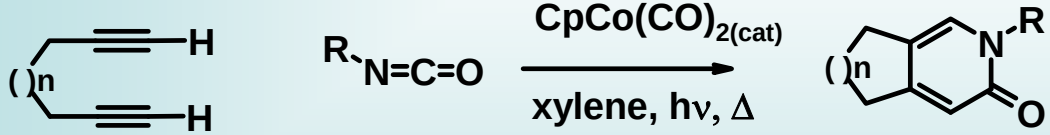
-the 'third' partner can also be a nitrile



n = 1-3

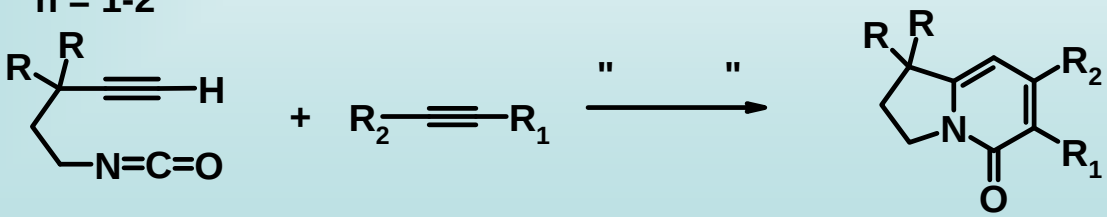
Vollhardt, K.P.C. et al *Tetrahedron* 1983, *39*, 905.

-or an isocyanate



n = 1-2

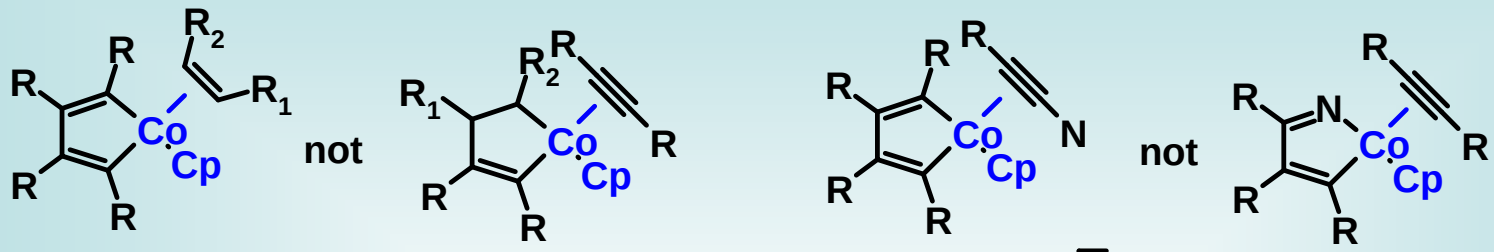
Earl, R.A.; Vollhardt, K.P.C.
J. Org. Chem. 1984, *49*, 4786.



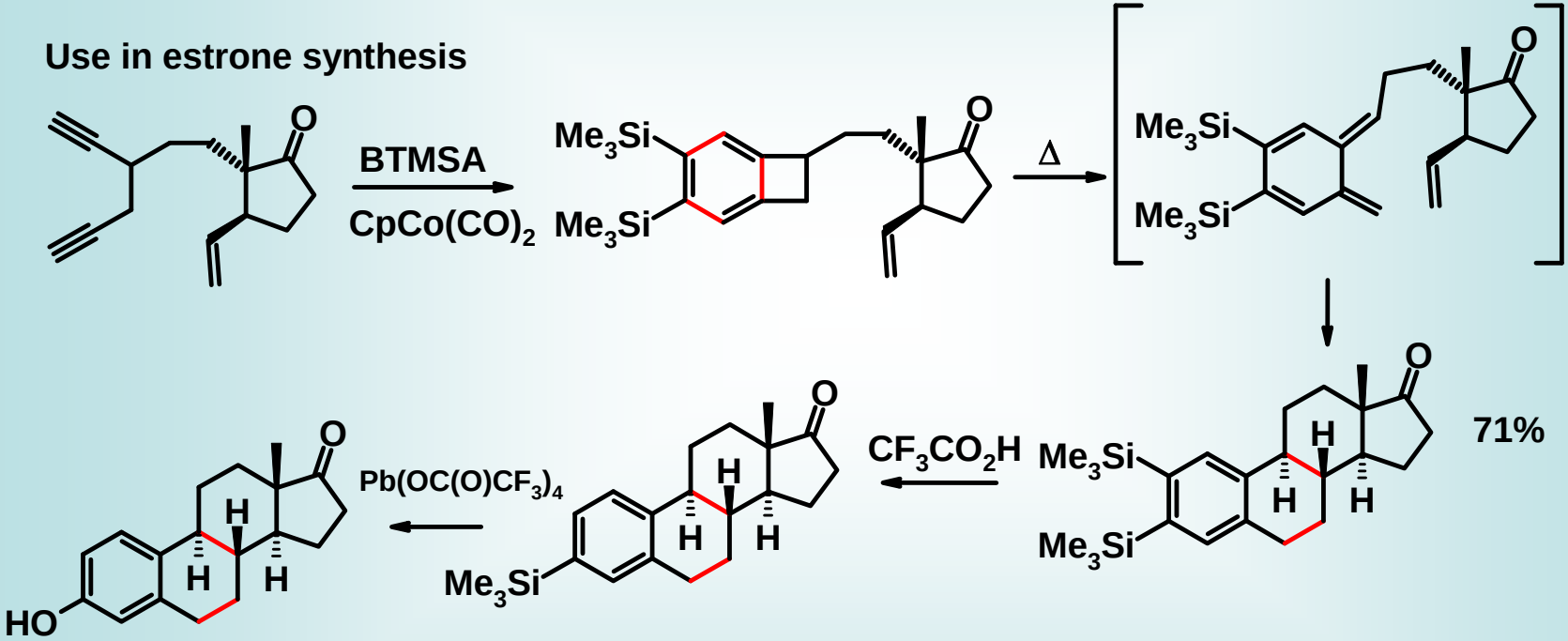
ca. 45%

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

i.e.



Use in estrone synthesis

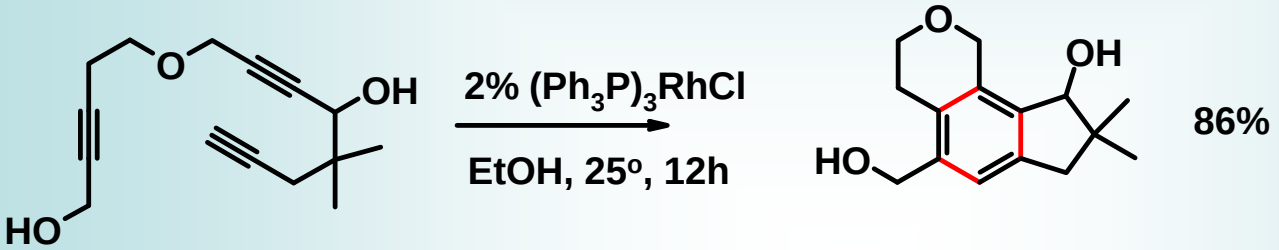


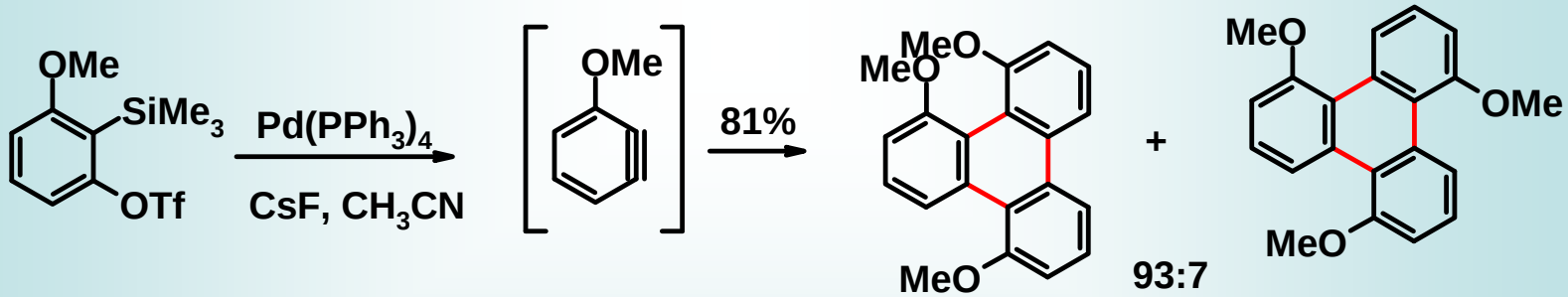
Funk, R.L.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* 1977, *99*, 5483; 1979, *101*, 215; 1980, *102*, 5253.

-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

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 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.