

## *Organocopper Chemistry*

Have a great historical importance, but still remain highly useful reactions. If not the first organometallic reactions developed they are among the first.

Most often used in conjugate addition reactions and couplings with  $sp^2$  carbons, but are also quite useful in epoxide openings,  $S_N2$  and  $S_N2'$  reactions, and alkyne additions.

While there are a few generalizations that can be made, this area is still quite empirical and experimentation is critical. Finding a close example in the literature is recommended.

We will discuss mechanism a bit, but the details are still debated and are not well understood.

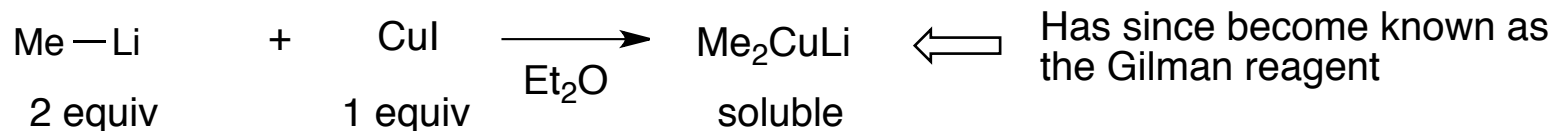
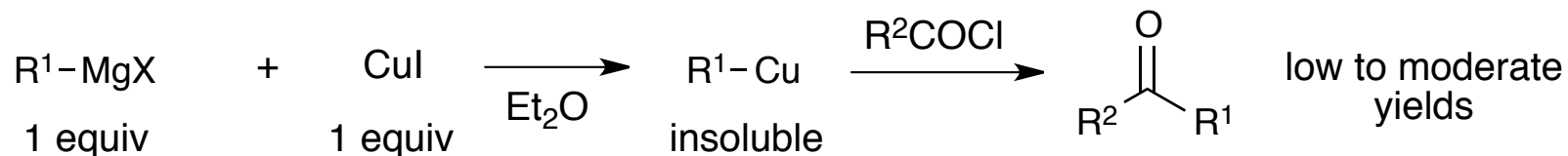
Most reactions are still run with stoichiometric amounts of Cu, but catalytic methods are becoming more important.

Lipshutz, B. H. Organocopper Chemistry, in *Organometallics in Synthesis: A Manual*, 2nd Ed; Schlosser, M., Ed.; Wiley: New York, 2002, pp 665–815.

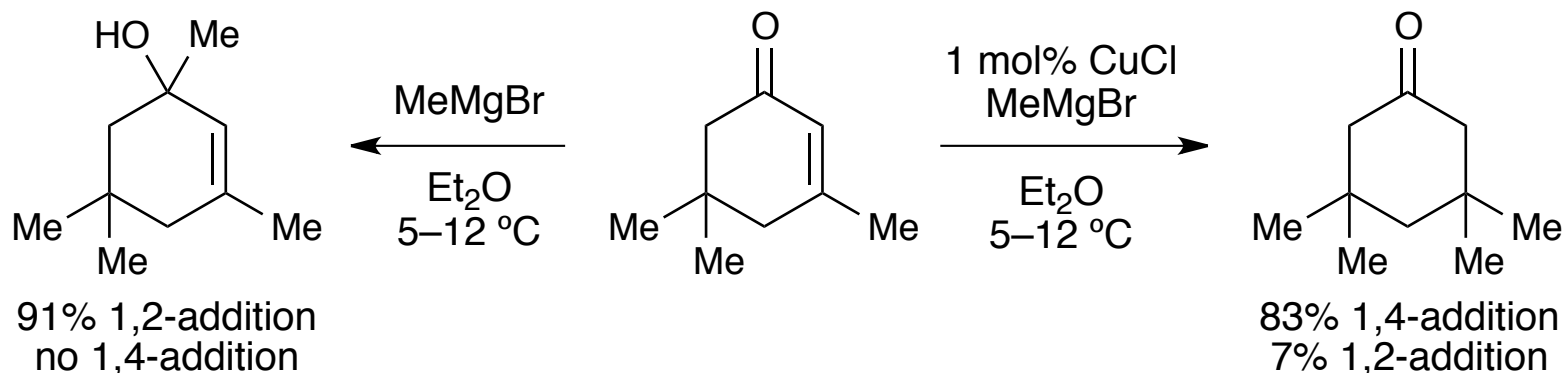
## Organocopper Chemistry – Initial Observations

Gilman, H.; Straley, J. M. *Recl. Trav. Chim. Pays-Bas Belg.* **1936**, *55*, 821–834.

Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630–1634.



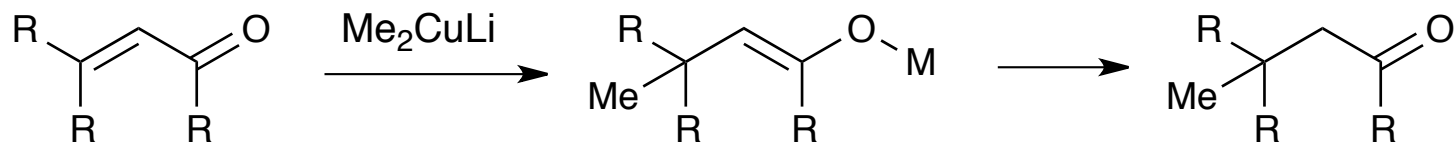
Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308–2316.



CuCl was unique, no other metal halide additive gave higher than ~5% 1,4-addition.

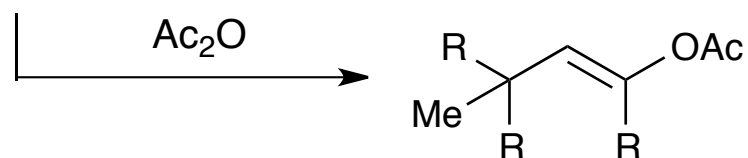
# Organocopper Chemistry – Key Reactivity Papers

House, H. O.; Respass, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128–3141.

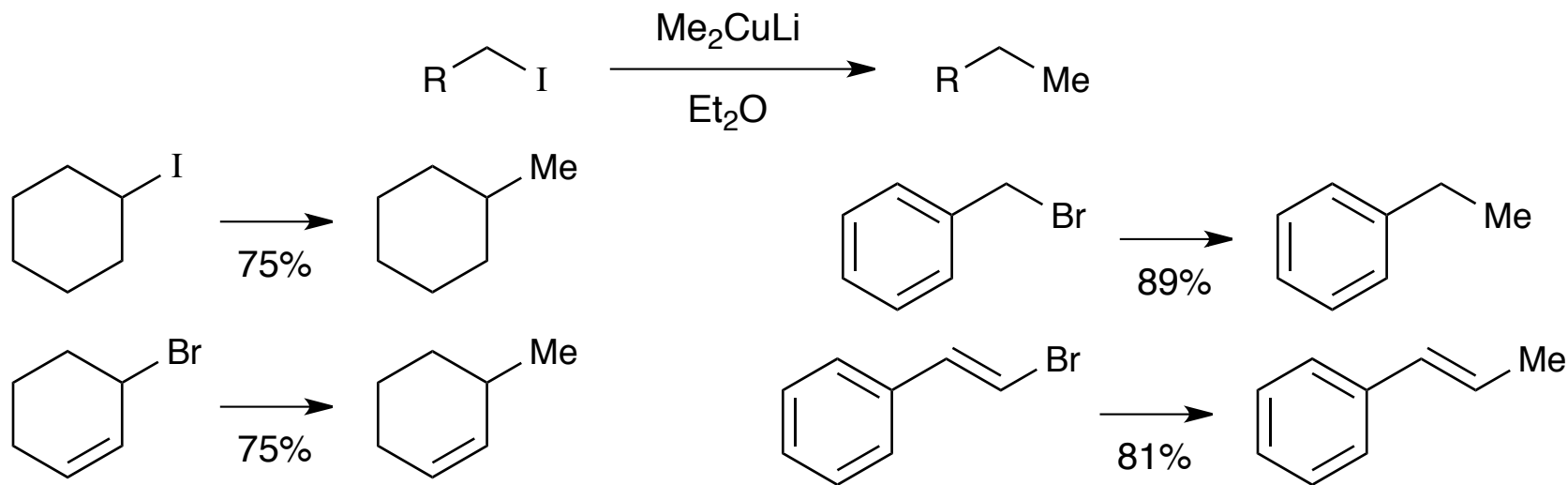


M = Li, MgBr, or Cu

high yields, with >99% 1,4-addition  
quick reaction times (<1 hr)



Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 3911–3912.



## Lower Order Gilman Cuprates – $R_2CuLi$

Soluble, thermally unstable; typically generate in situ; often the "recipe" used to make the reagent and/or react with substrate is critical to success; often discovered empirically

Can utilize and transfer virtually any  $sp^2$  or  $sp^3$  hybridized carbon

Because of low basicity, diorganocuprates undergo alkylation reactions with a variety of organic electrophiles; generally with high levels of inversion and little elimination; typically reacts in  $S_N2'$  manner if available

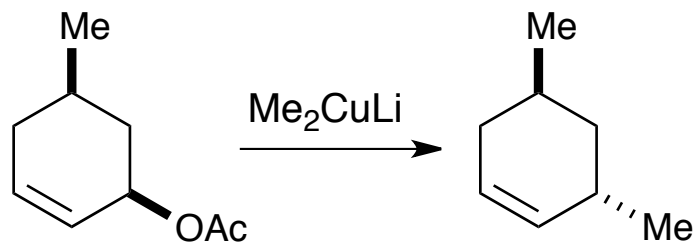
### order of reactivity

primary > secondary >> tertiary      iodide > bromide > chloride

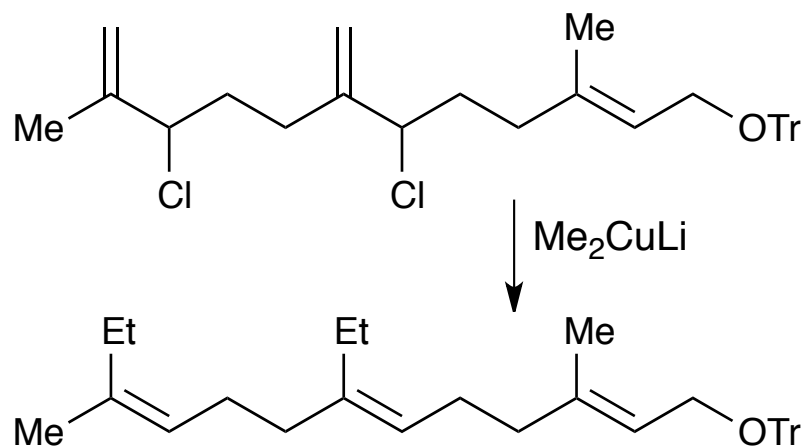
alkenyl halides and triflates work as well, with retention of configuration (*cis*, *trans*)

$RCOCl$  > aldehydes > tosylates ~ epoxides > iodides > ketones > esters > nitriles

Some examples:



*J. Am. Chem. Soc.* **1976**, *98*, 7854



*J. Am. Chem. Soc.* **1970**, *92*, 737

## Lower Order Gilman Cuprates – $R_2CuLi$

Undergoes conjugate addition reactions with  $\alpha,\beta$ -unsaturated electrophiles; the intermediate enolate can be trapped with a variety of electrophiles

Ketones – most reactive, only slightly diminished rates with substitution at  $\alpha$  or  $\beta$  position

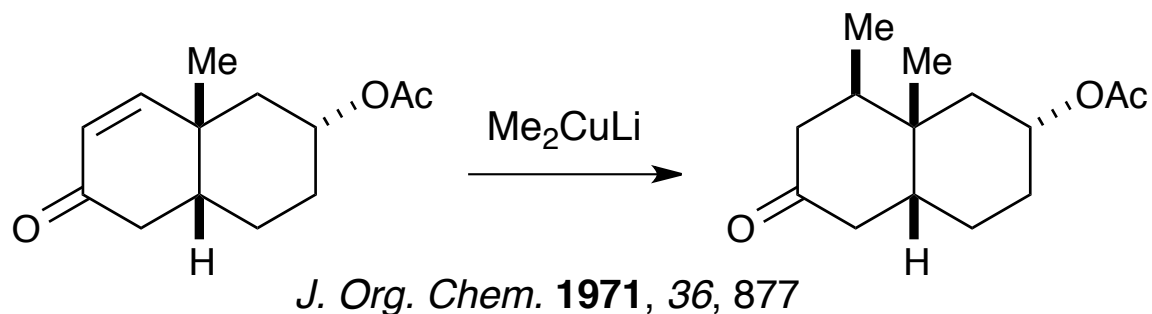
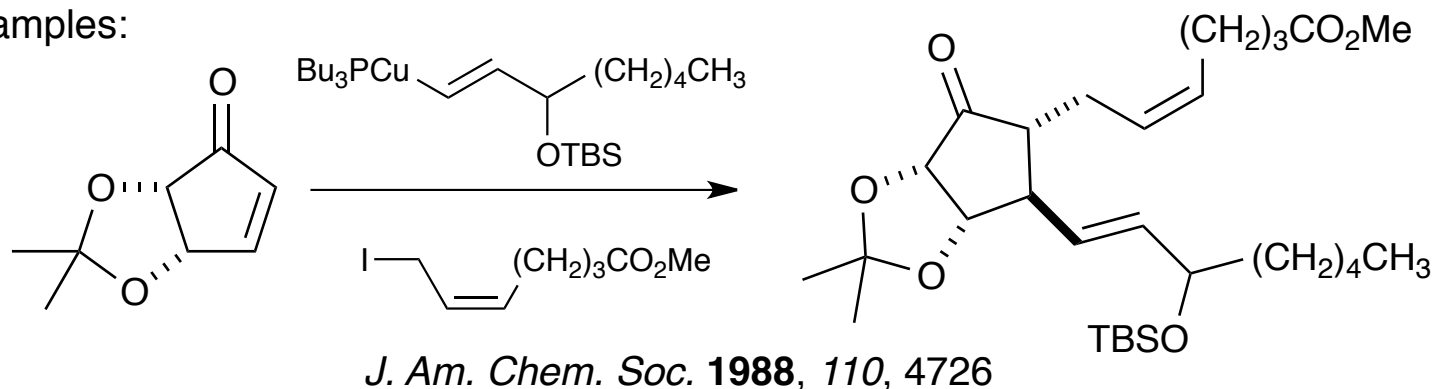
Esters – less reactive than ketones, dramatically lower rates with substitution at  $\alpha$  or  $\beta$  position

Esters – less reactive than ketones, dramatically lower rates with substitution at  $\alpha$  or  $\beta$  position

Sulfones are competent substrates; carboxylic acids do not react; amides and anhydrides have seen limited work; aldehydes see competing 1,2-addition

Addition of phosphine ligands can often speed up troublesome reactions

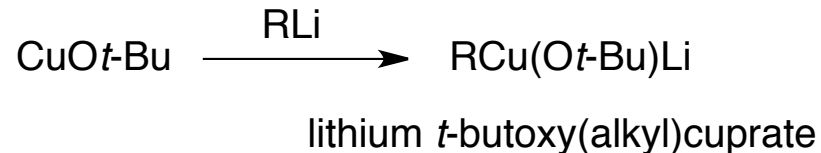
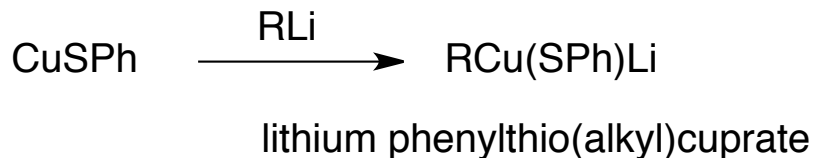
Some examples:



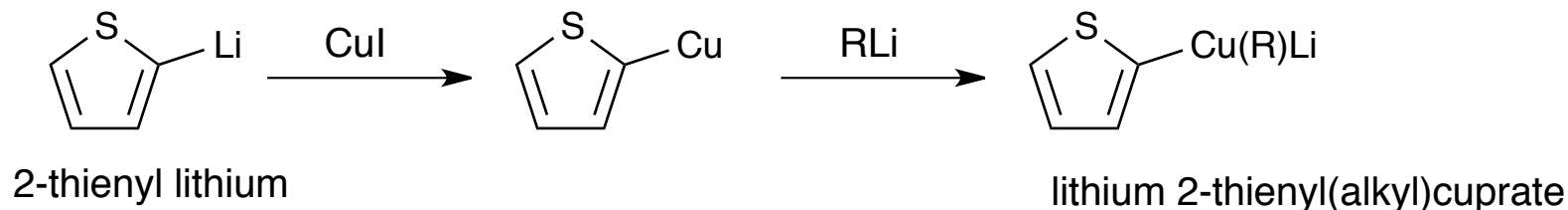
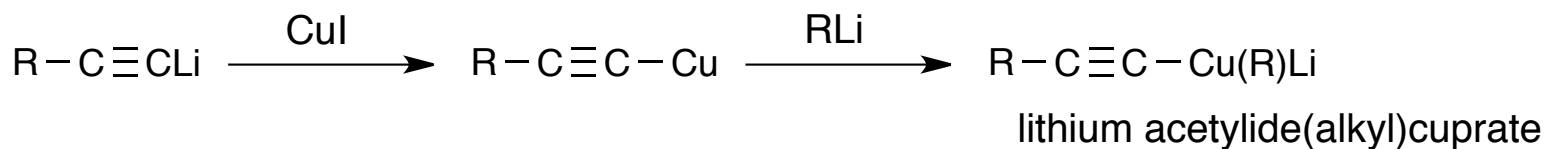
## Lower Order Mixed Cuprates – $R_fR_rCuLi$

A major problem associated with Gilman-type organocuprate reagents is that they require two alkyl groups, but only transfer one. This is particularly problematic when wanting to transfer "precious" alkyl groups. Also can be quite unstable, so excess reagent often needed.

To address this problem modified reagents have been developed with one "transferable" group and one "residual" group. These are often stable at higher temps ( $-20\text{ }^\circ\text{C}$  and  $0\text{ }^\circ\text{C}$ ). Often the reactivity is altered (for better or worse) relative to Gilman-type reagents. Best to compare with known systems.



Can also have mixed "alkyl"cuprates with spectator ligands (these are most popular):



## Lower Order Mixed Cuprates – $R_fR_rCuLi$

Can also use P- and N-based ligands; these are especially stable (still reactive after 24 hrs @ rt)

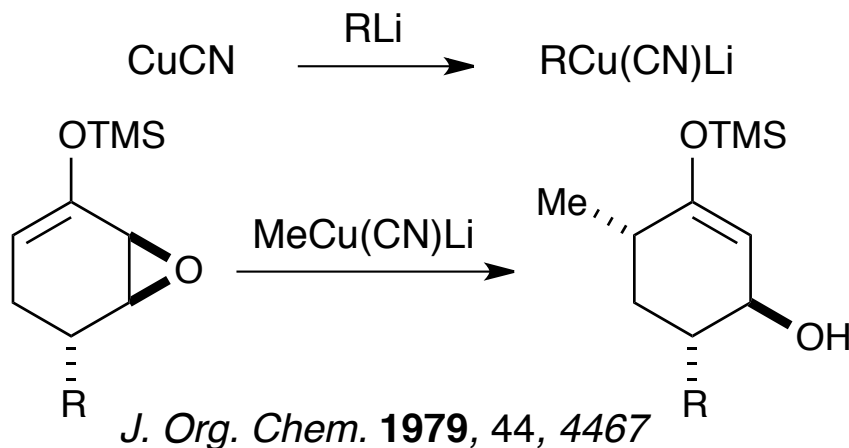


*J. Am. Chem. Soc.* **1982**, 104, 5824

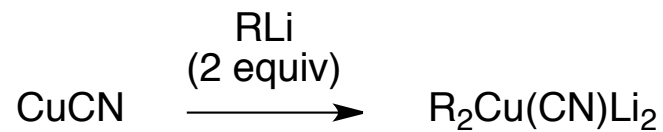
*J. Org. Chem.* **1984**, 49, 1119



lower order cyanocuprates, ease of preparation (start from CuCN), but less reactive than other mixed cuprates, but are quite useful in epoxide openings



"Higher order cyanocuprates" can be made by addition of two equivalents of RLi to CuCN; Brings reactivity more in line with Gilman reagents, but are still more stable

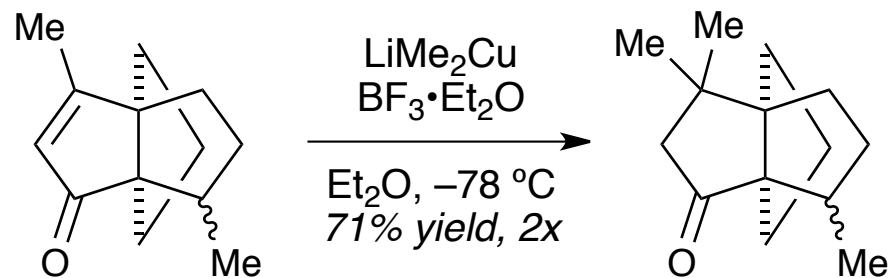


## Additives – $BF_3 \cdot Et_2O$

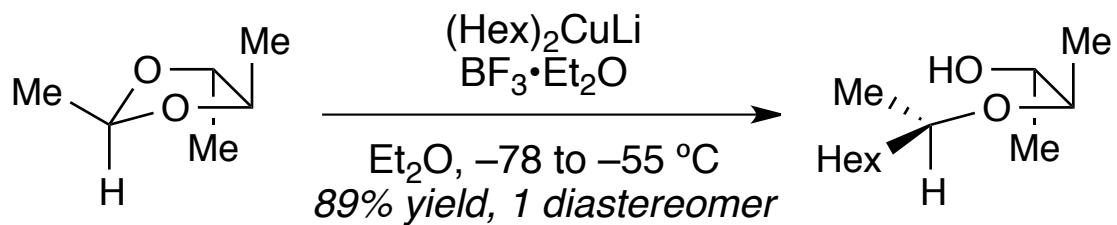
If the cuprate of choice is unreactive at low temperature and especially unstable at higher temperatures, the use of  $BF_3 \cdot Et_2O$  or  $Me_3SiCl$  may improve reactivity.



*J. Am. Chem. Soc.* **1989**, *111*, 1351



*J. Org. Chem.* **1982**, *47*, 1845

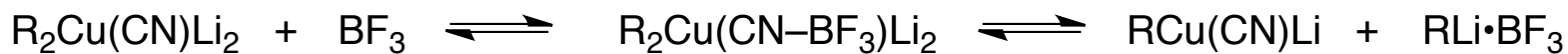


*Tetrahedron Lett.* **1984**, *25*, 3083

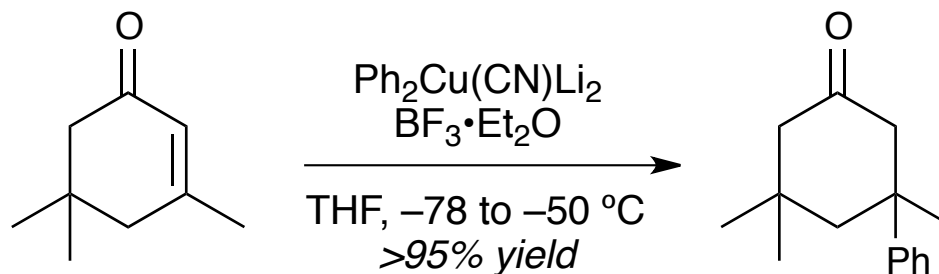


## Additives – $BF_3 \cdot Et_2O$

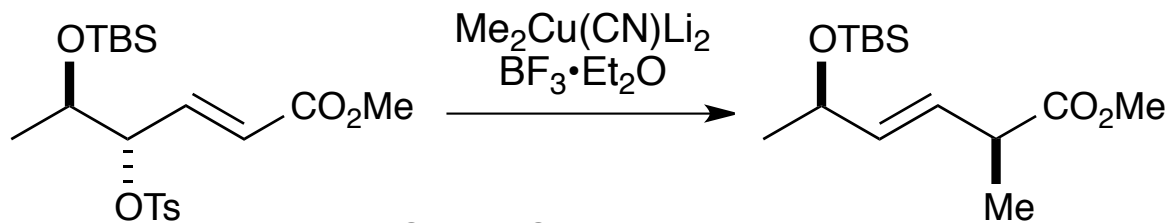
with cyanocuprates the effect is more complex and likely involves coordination of the  $BF_3$  to the nitrile at some point.



*J. Am. Chem. Soc.* **1988**, *110*, 4834



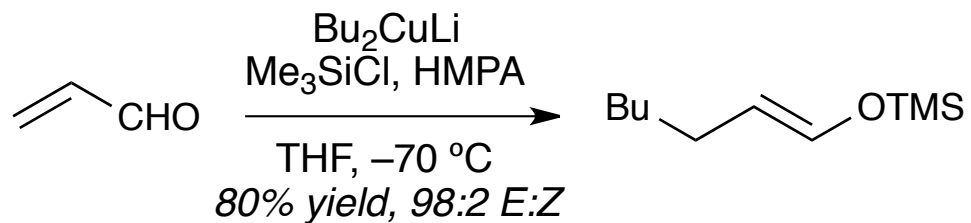
*Tetrahedron Lett.* **1984**, *25*, 5959



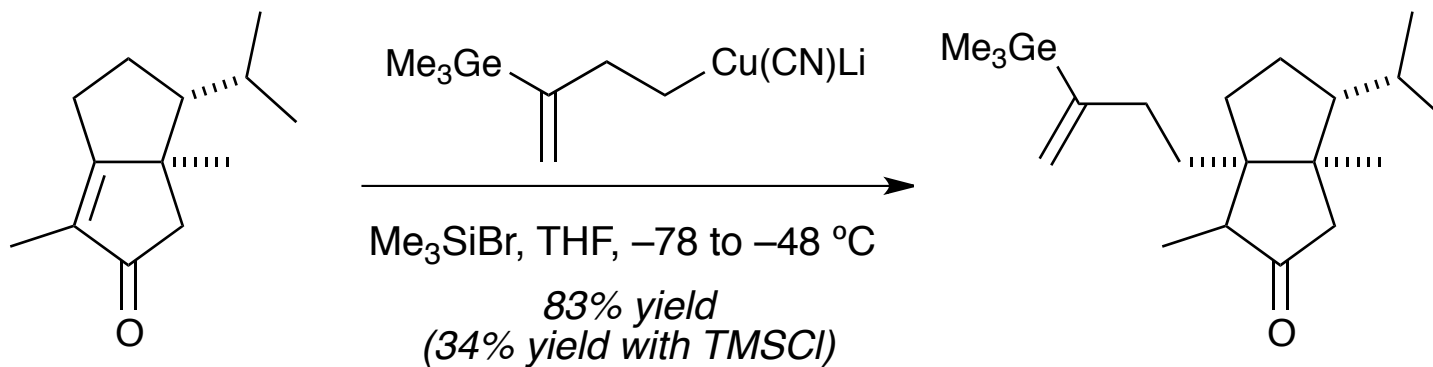
*J. Am. Chem. Soc.* **1986**, *108*, 7420

## Additives – $\text{Me}_3\text{SiCl}$

Exactly how  $\text{Me}_3\text{SiCl}$  modifies the Gilman reagents is debated;  $\text{Me}_3\text{SiBr}$  can also be used and may give improved benefit



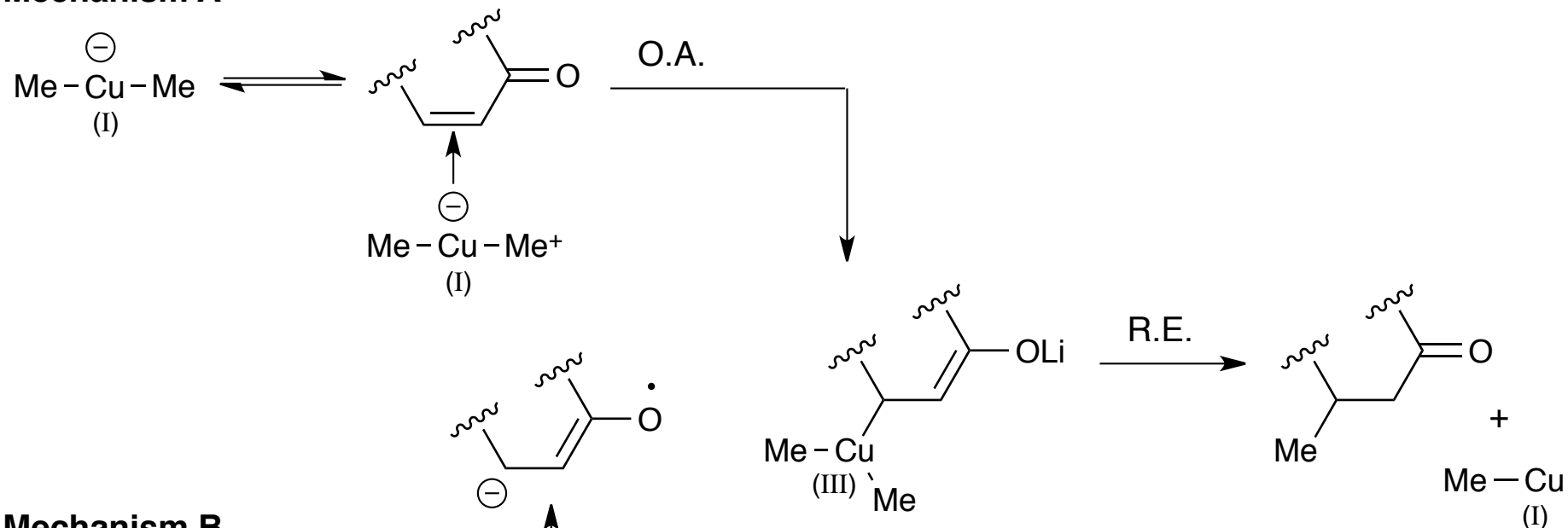
*Tetrahedron* **1989**, 45, 349



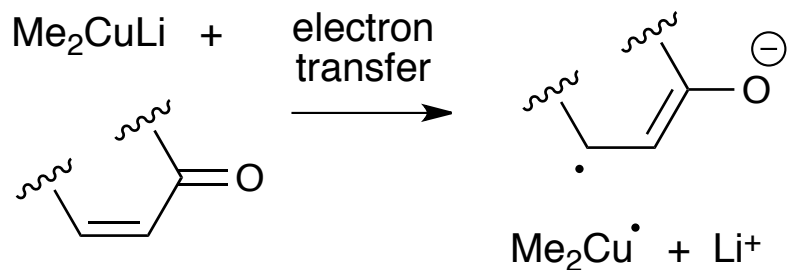
# Mechanistic Studies

The question of how cuprates undergo 1,4-addition has been greatly debated over the years.

## Mechanism A



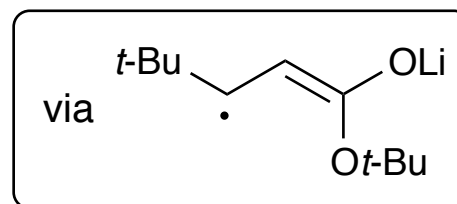
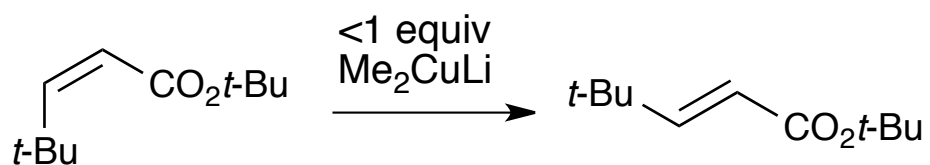
## Mechanism B



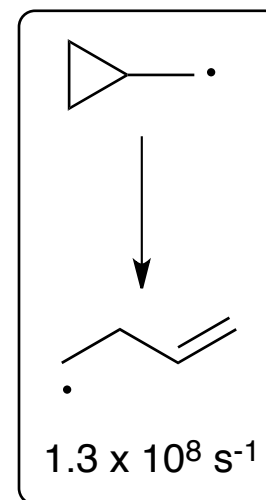
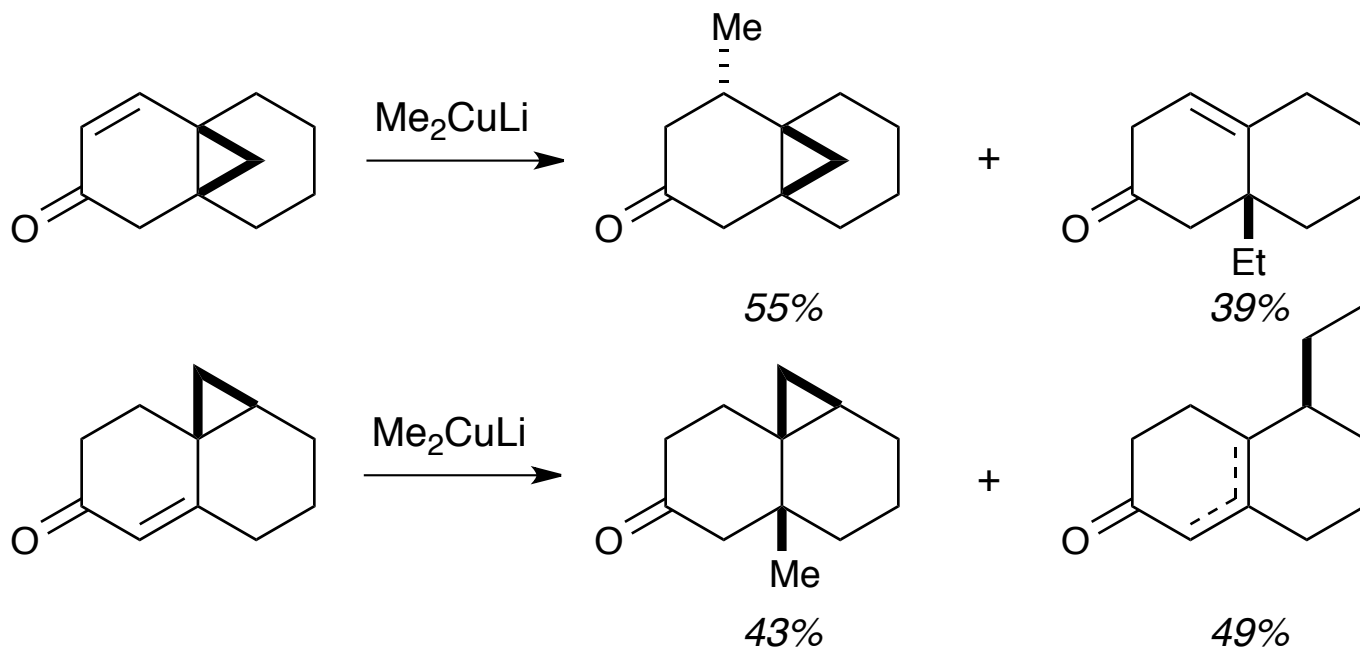
$\pi$ -complexes and Cu(III) intermediates have been observed by NMR, see:  
*J. Am. Chem. Soc.* **2002**, *124*, 13650  
*J. Am. Chem. Soc.* **2007**, *129*, 7208  
*J. Am. Chem. Soc.* **2007**, *129*, 11362

# Mechanistic Studies – Evidence for Radical Pathway

Isomerization without conjugate addition



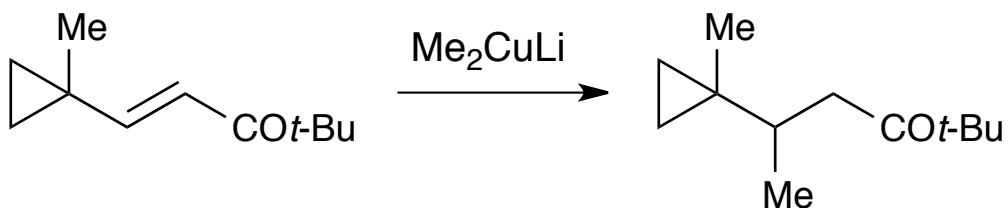
Radical clocks



*Tetrahedron Lett.* **1971**, 2875.

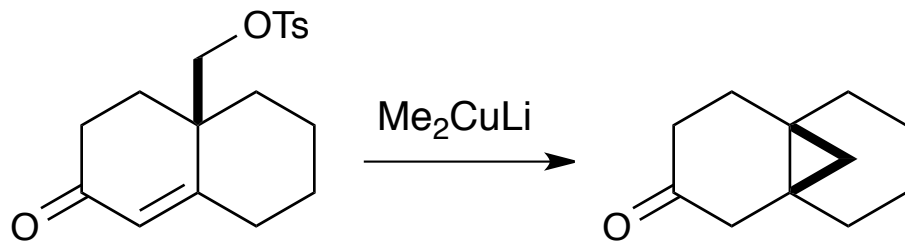
## Mechanistic Studies – Evidence for Radical Pathway

Radical clocks, cont'd



radical anion intermediate is very rapidly trapped by cuprate reagent, or mechanism change is occurring

Trapping of radical anion



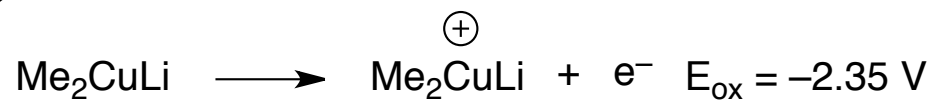
no conjugate addition observed

*Tetrahedron Lett.* **1975**, 187

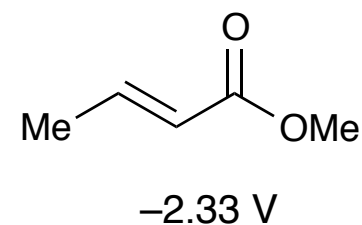
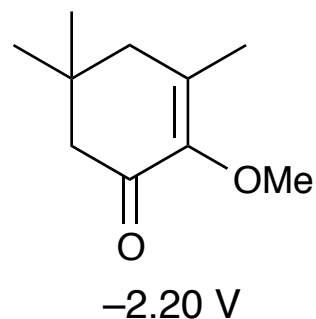
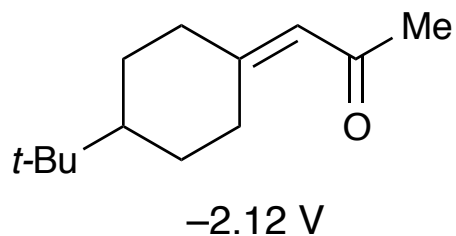
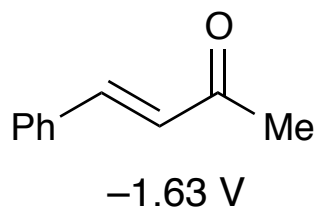
# Mechanistic Studies – Evidence for Radical Pathway

Reduction potentials

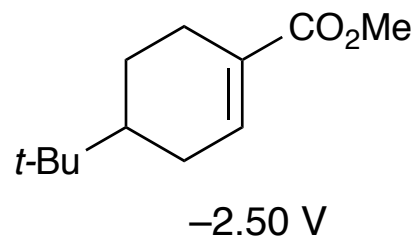
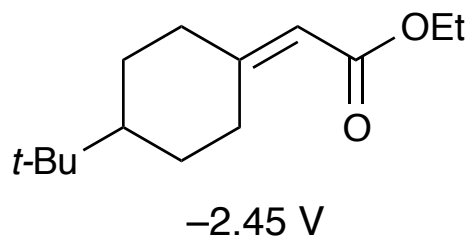
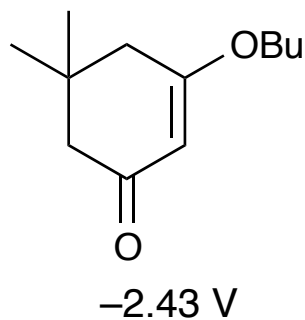
*J. Am. Chem. Soc.* **1972**, *94*, 5495



Substrates that react (78–98% yield) and their  $E_{\text{red}}$



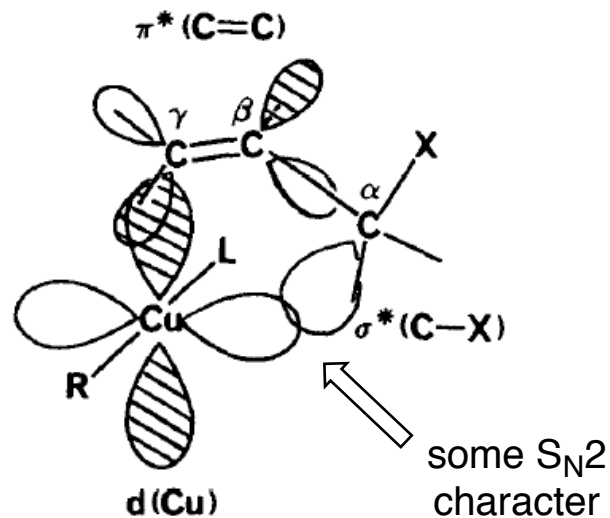
Substrates that don't react (>90% recovery) and their  $E_{\text{red}}$



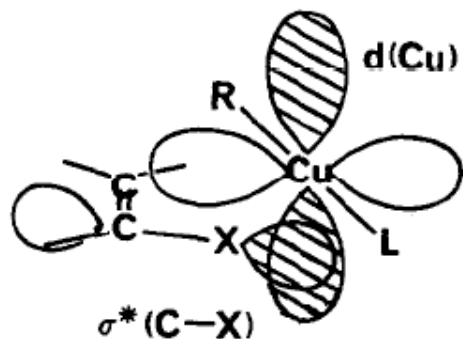
# Orbital Picture

Both conjugate additions and  $S_N2'$  reactions can be explained by  $d \rightarrow \pi^*$  interactions

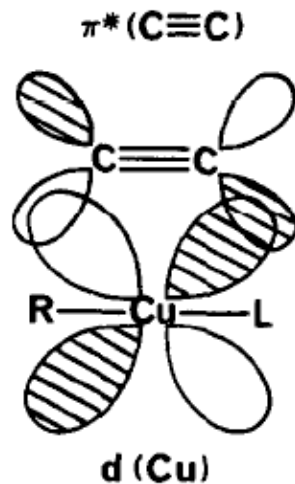
electron repulsion in highly occupied d orbitals of Cu make them quite diffuse and sterically accessible



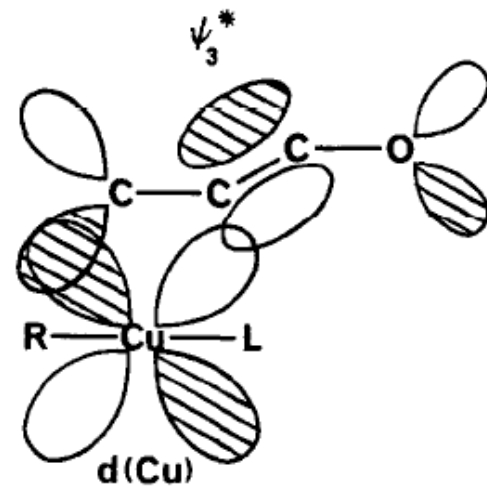
*anti-S<sub>N2'</sub>* in allylic systems



cross-coupling reactions



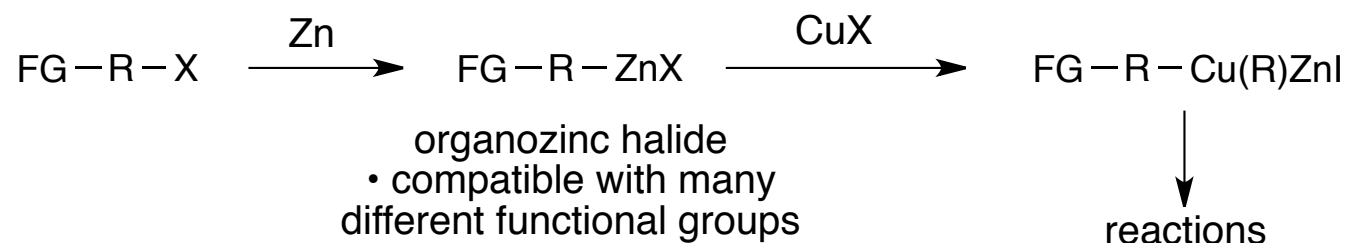
addition to alkynes



conjugate additions

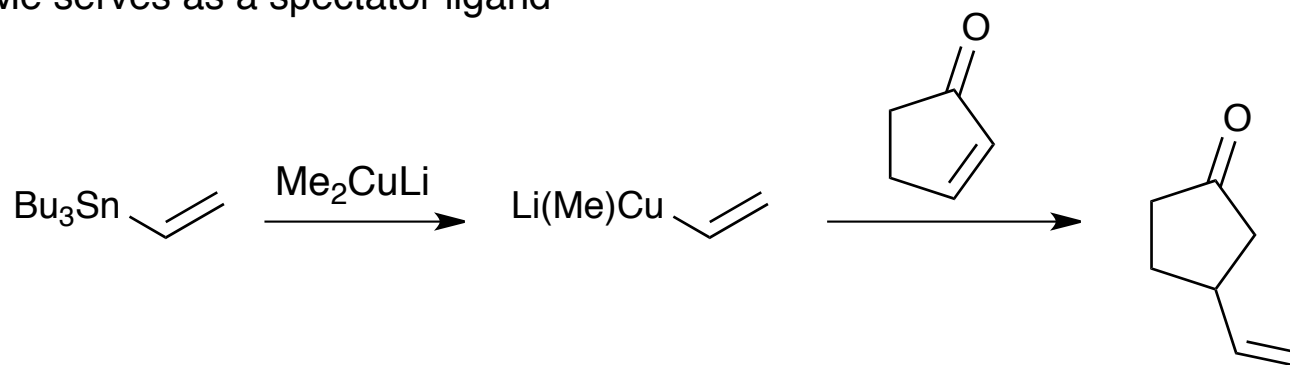
## Transmetallation Onto Copper

"Functionalized" cuprates can be prepared through transmetallation routes



copper sources:  $\text{CuCN}\cdot 2\text{LiCl}$ ,  $\text{Cu}(\text{OTf})_2$ ,  $\text{CuBr}\cdot \text{SMe}_2$   
compatibility of zinc species allows catalytic copper to be used in many cases

Transmetallation from other organometals (M=Sn, Zr, Al, Te) possible as well, many times  $\text{Me}_2\text{CuLi}$  is used and Me serves as a spectator ligand

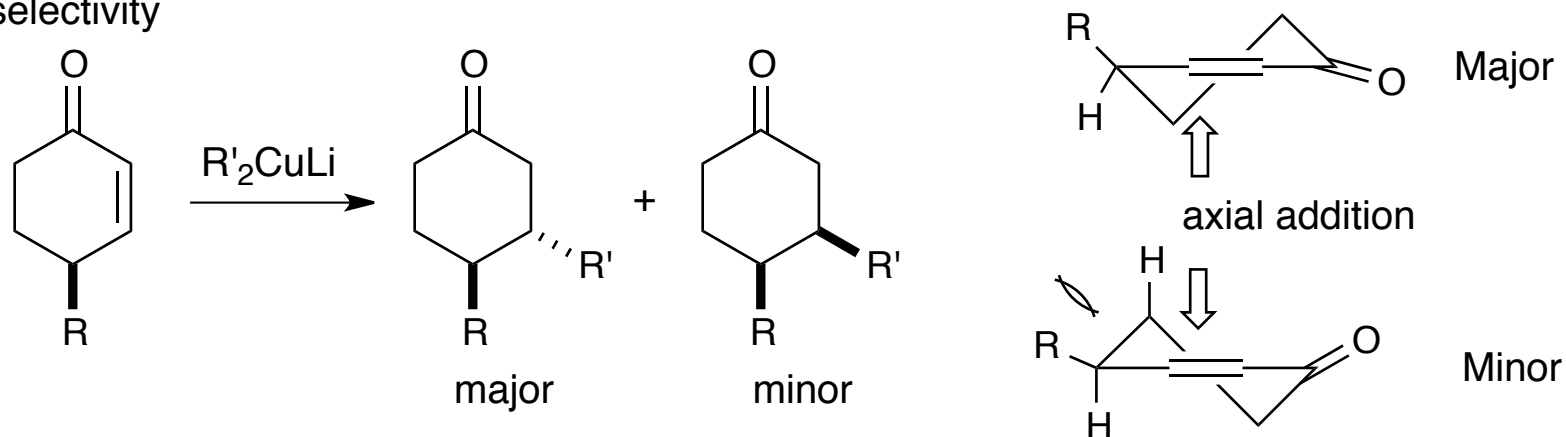




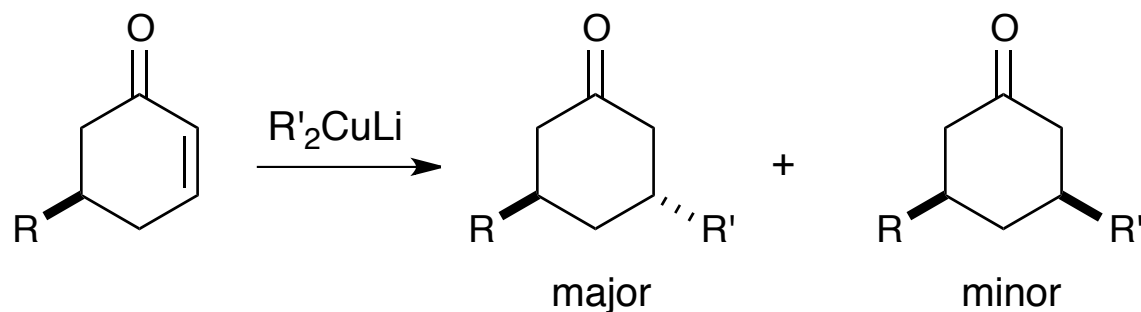
# Stereoselection

Diastereoselectivity can generally be predicted with existing models and chair-like transition states

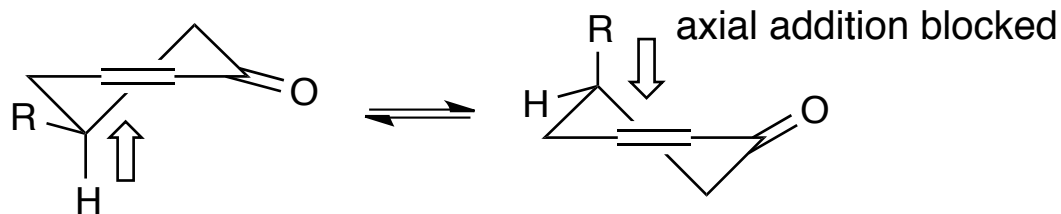
3,4-selectivity



3,5-selectivity

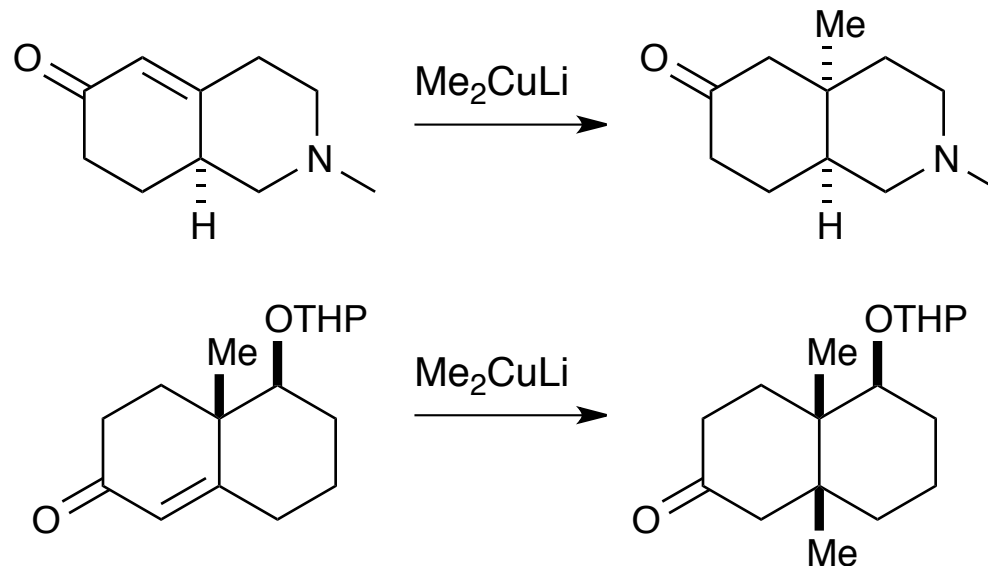


both conformations approximately equal, but only one is reactive



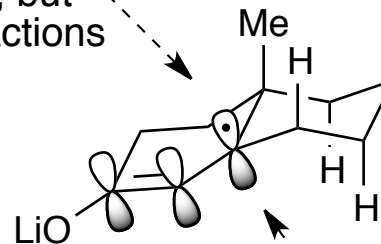
# Stereoselection

Fused rings



consider the radical anion intermediate

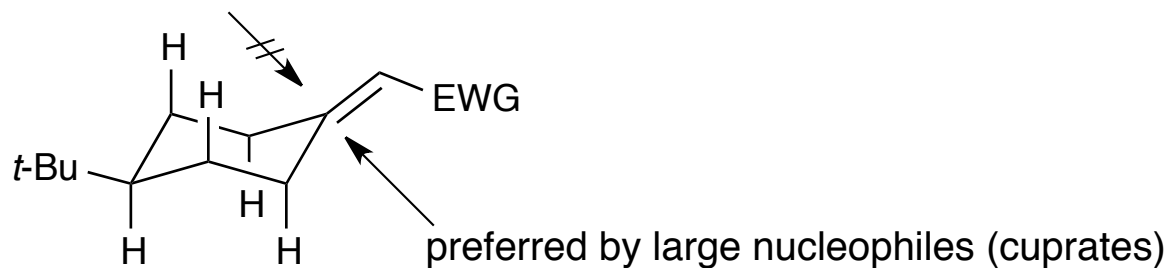
"Equatorial" approach favored by large nucleophiles (cuprates), but slowed by 1,2-torsional interactions



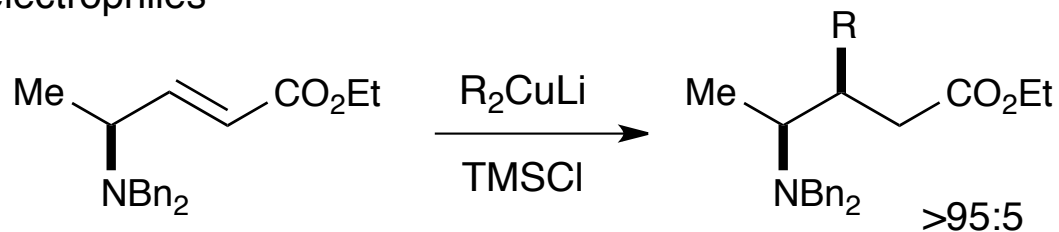
"Axial" approach disfavored by large nucleophiles due to 1,3-diaxial interactions

# Stereoselection

exocyclic olefins



acyclic electrophiles



*Angew. Chem. Int. Ed. Engl.*  
**1989**, 28, 1706

