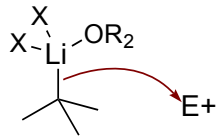
Topic 14: Alkali Organometallics



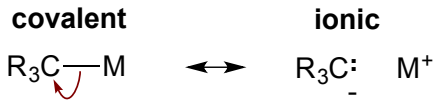
Read:

F. A. Carey & R. J. Sundberg Advanced Organic Chemistry, Part A: Structure and Mechanisms. 5th Ed. **Ch. 6**

M. Schlosser, Ed. *Organometallics in Synthesis: A Manual* Wiley, 1994. "Chapter 1. Organoalkali Reagents"

Misconception

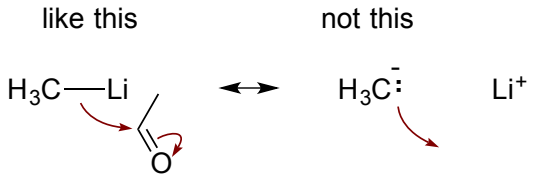
■ Consider these two resonance forms:



■ Electronegativity determines ionic character & basicity

Electronegativity:	**2.2**	**1.3**	**0.98**	**0.93**	**0.82**	**0.82**	**0.79**
R-M Covalent character:	**H** >	**Mg** >	**Li** >	**Na** >	**K** >	**Rb** >	**Cs**
(Ionic character) Basicity:		**R-MgBr** <	**R-Li** <	**R-Na** <	**R-K**	<	**R-Cs**
		R—MgBr	R—Li	R—Na	R—K		R—Cs

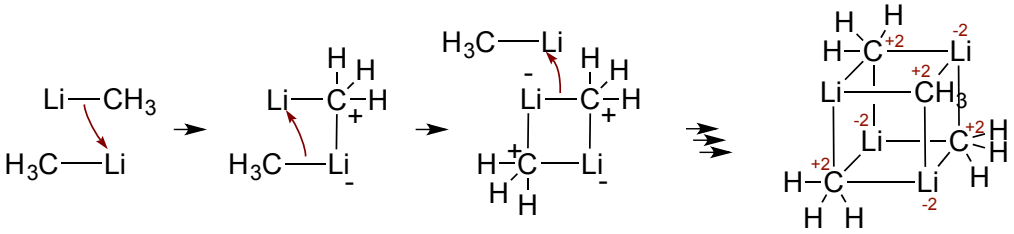
■ **Avoid** ionizing R-M bonds; just use the bond as the base/nucleophile.



■ **COMPLETE FICTION**: Li, Na, K, Mg, Ca, etc. want no electrons

They want 8 valence electrons!

Here's what H_3CLi does in hexane.



Lewis structure

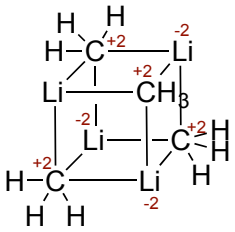
Formal charges: Li^{2-}, C^{2+}

3 bonds to each Li

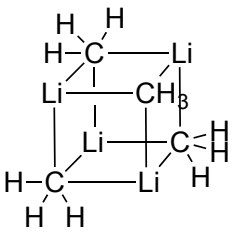
6 bonds to each C

Aggregation of Alkali Organometallics

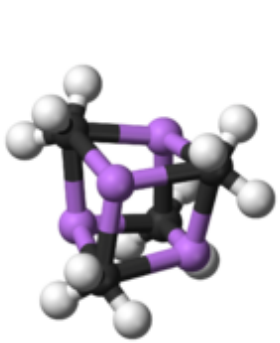
■ Alkyllithiums aggegrate to form tetramers, hexamers, etc. to help lithium satisfy the octet. Sterics often prevents Li from achieving an octet. Bulkier alkyl groups lead to less aggregation. Using dative bond representations reduces the complexity of these structures.

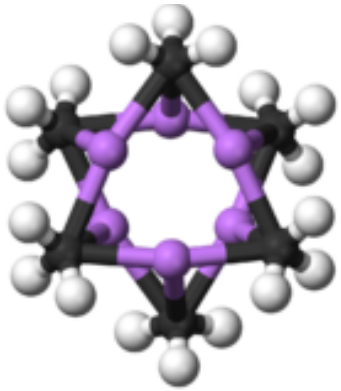


Lewis structure



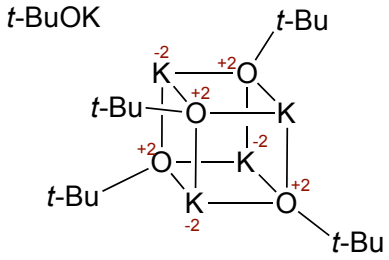
dative bonds

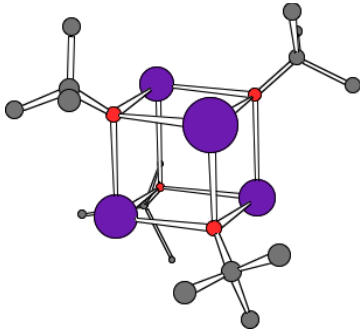


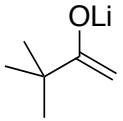


crystal structures of $(MeLi)_n$

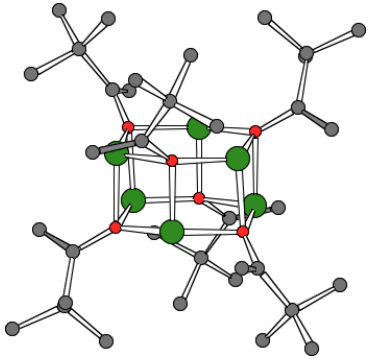
■ Metal alkoxides also aggregate







=

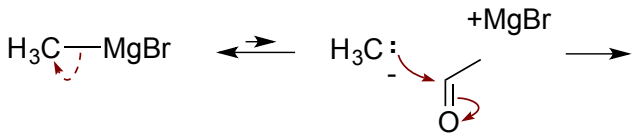


■ You don't have to draw these aggregrates; but never be afraid to form additional bonds to alkali metals.

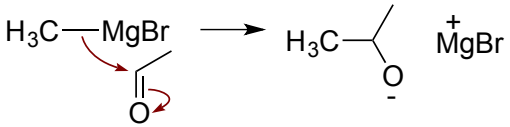
Dos and Don'ts for Drawing Mechanisms with Organoalkali Species in Chem 201

■ Draw arrow-pushing mechanisms that avoid ionizing anions and cationic metals

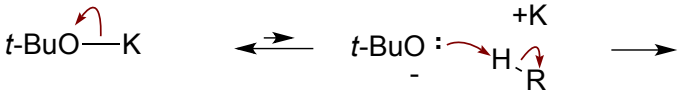
Don't do this:



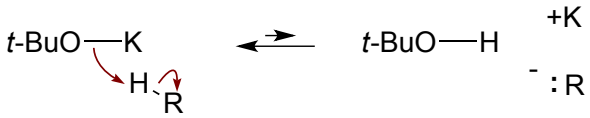
Do this:



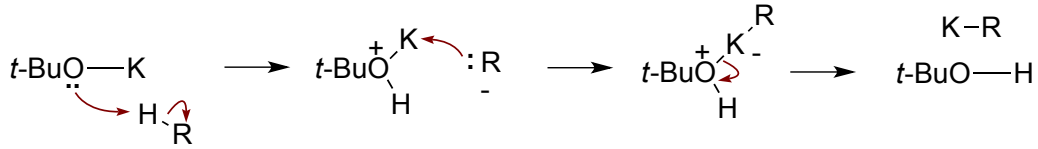
Don't do this:



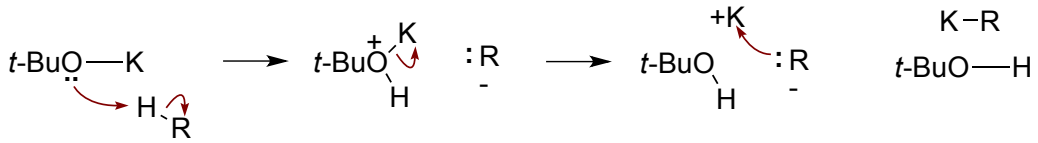
Don't do this:



Do this:



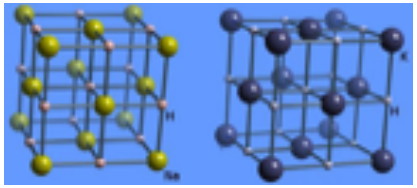
I'll accept..



Metal Hydrides

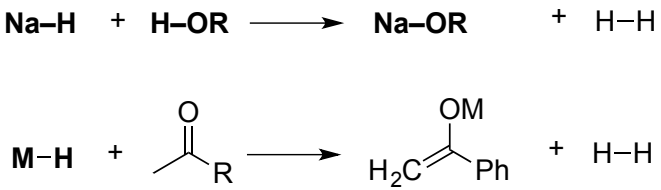
■ **Na—H = cubic lattice**

(**Arrow pushers**: pretend M—H is a monomer)



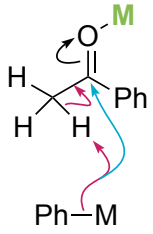
Dyck, W.; Jex, H. *J. of Physics C* **1981**, 14, 4193

■ Example: **metal hydride basicity**

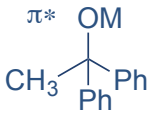


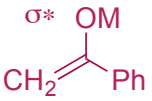
MH	k_{rel}
Li-H	1
NaH	1,000
KH	1,000,000

■ Basicity (vs nucleophilicity) increases from RMg to RK.



Ph-M →





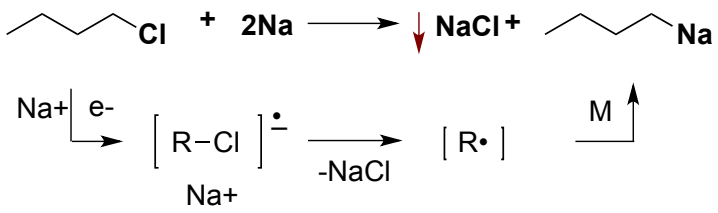
Ph—MgBr	**97**	**0**
Ph—Li	**14**	**75**
Ph—Na	**4**	**60**
Ph— K	**0**	**67**

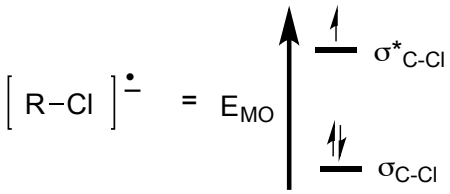
more negative charge = more basic

Grovenstein, E. *JACS* **1959,** 4842

Synthesis of Organometallics

■ We don't have arrow pushing representations for electron transfers, nor good Lewis representations for the radical anion intermediates.

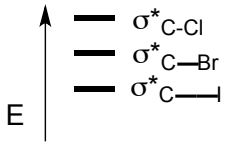




■ Rates depend on R-X: **RI > RBr > RCl**

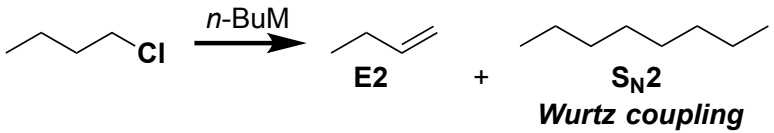
Why rel. order?

Step 1 = e- into σ* orb



Why don't we make *n*-BuNa?

■ Kronos behaviour *(children swallowed by creator)*

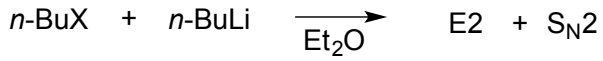


Rates: R-K > R-Na > R-Li > R-MgBr

impractical

Formation of R-Na requires *special conditions:*
(finely dispersed Na, high speed stirrer, vortical fluid motion, special glass, -10 °C)

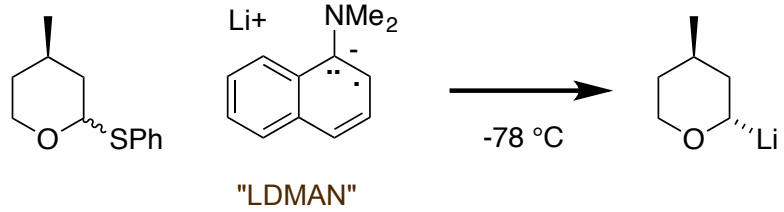
■ Always make R–Li from R—Cl but not R — I. Here's why…



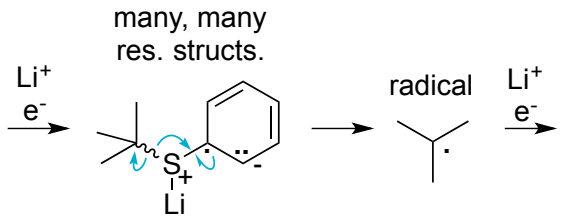
X	$t_{1/2}$	$t_{1/2}$	
Cl	40 h	>100 h	in C_6H_6...
Br	30 min	40 h	
I	< 5 min	3 h	

Preparation of Alkyllithiums by Reductive Lithiation

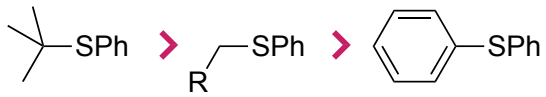
■ **Reductive lithiation** of thiophenyl ethers. Li + naphthalene = LiNp, but it is a pain to remove one equivalent of naphthalene after the reaction is over. Dimethylaminonaphthylamine is readily removed with an acid wash.



■ LiNp efficiently adds an electron to the pi* antibonding orbital of PhS groups. Rates of reductive lithiation correlate with the ease of radical formation.



rate of reductive lithiation:



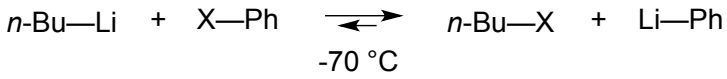
Cohen, T. *J. Am. Chem. Soc.* **1984,** *106*, 1130.

Preparation of Alkyllithiums by Exchange Reactions

■ Metal/halogen exchange

Rates depend on R-X: **RI > RBr > RCl**

With R-I, **instantaneous at -80 °C**

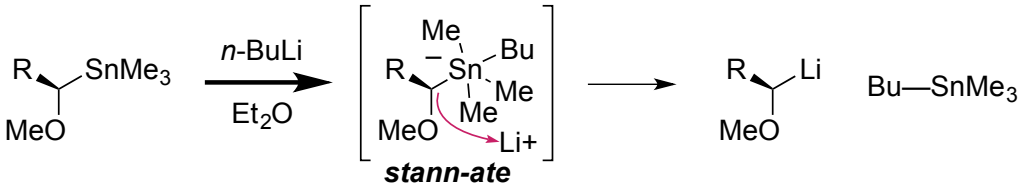


Mechanisms: Newcomb, M. *TL*, **1989**, *26*, 1183
R-I, low temp - iodate; R-Br, high temp = e- transfer

Rates: I >> Me_3Sn > Me_3Sn
80 : 1

Kanda, T *J. Phys. Org. Chem.* **1996**, *9*, 29.

■ Sn-Li exchange (same with lithium-iodide exchange)



Mechanism = stann**"ate"**

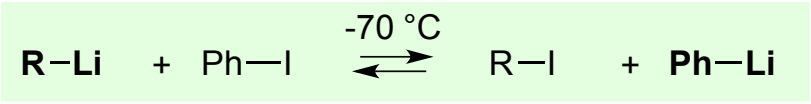
Sn: MacDonald, T. *J. Am. Chem. Soc.* **1988**, *110*, 842.
I: Farnham, W. B. *J. Am. Chem. Soc*, **1986**, *108*, 2449.

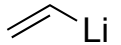
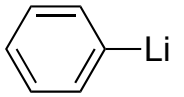
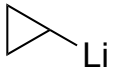
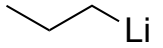
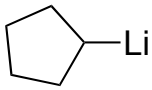
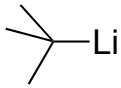
■ Sn-Li exchange proceeds with retention at carbon

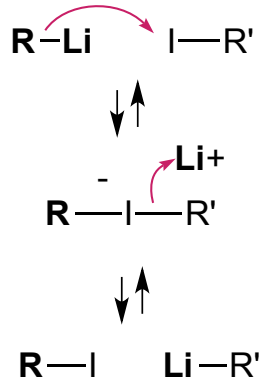
Reich, H *J. Am. Chem. Soc.* **1992**, *114*, 6577-9.

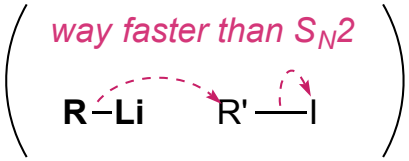
Metal-Halogen Exchange Driven by Thermodynamics

■ Metal-halogen exchange is faster than S_N2 (at low temp.)



Compound	K_{eq}
	**0.004**
	**1**
	**10**
n-BuLi ~ 	**7,500**
s-BuLi ~ 	**10,000,000**
	**>10,000,000**

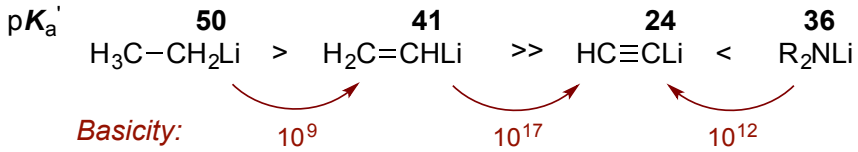




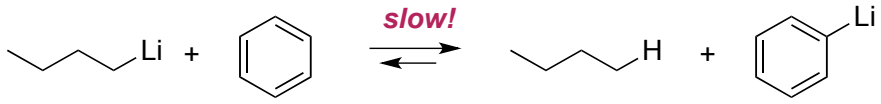
Applequist, D.E.; O'Brien, D. F. "Equilibria in Halogen-Lithium Interconversions" *J. Am. Chem. Soc.*, **1963**, *85*, 743-748.

Formation of Organometallics by Metalation

■ **Recall:**

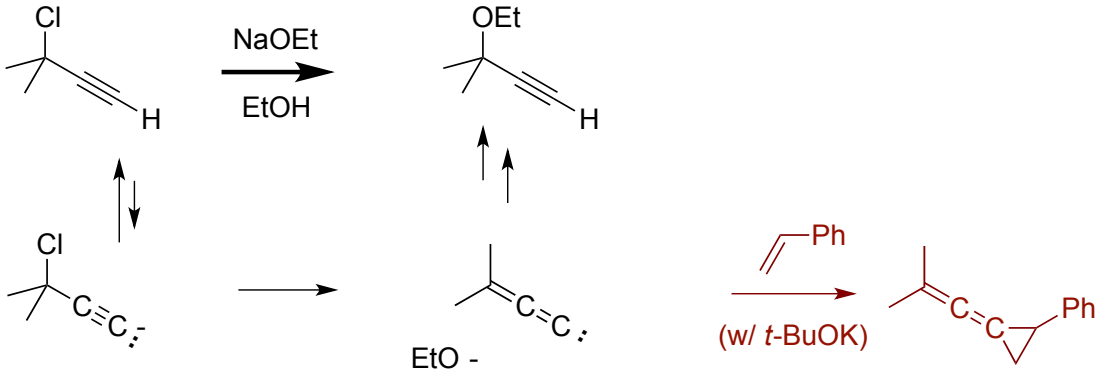


■ Direct metalation (deprotonation) of benzene is **too slow** to be useful



■ Alkynes can be directly metalated ...also with BuLi

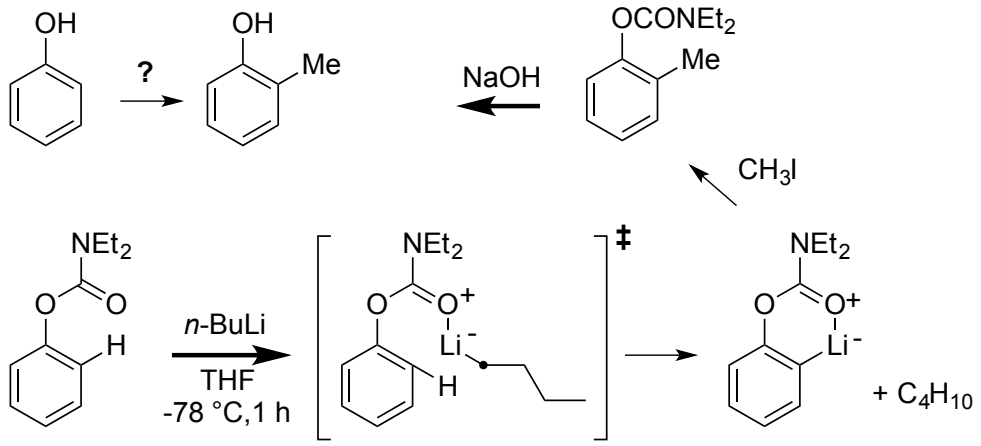
■ Recall: deprotonation of alkyne C-H is relatively fast



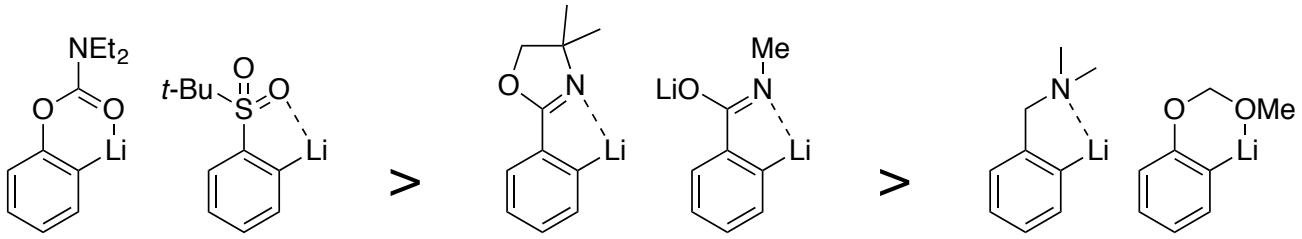
Shiner, V. J.; Humphrey, J. S., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 622.
See also… Sonogashira couplings

Directed Ortho Metalation

■ **Chelation of R-Li** speeds up metalation and stabilizes Ar-Li



■ Relative directing power; (you keep the chelate in the aryllithium)

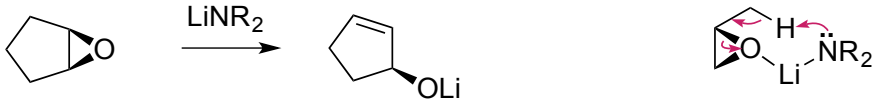


V. Snieckus
"Directed ortho metalation. Tertiary amide and *O*-carbamate directors in synthetic strategies for polysubstituted aromatics"
Chem. Rev. **1990**, *90, 879.*

Metalation of Strained Rings

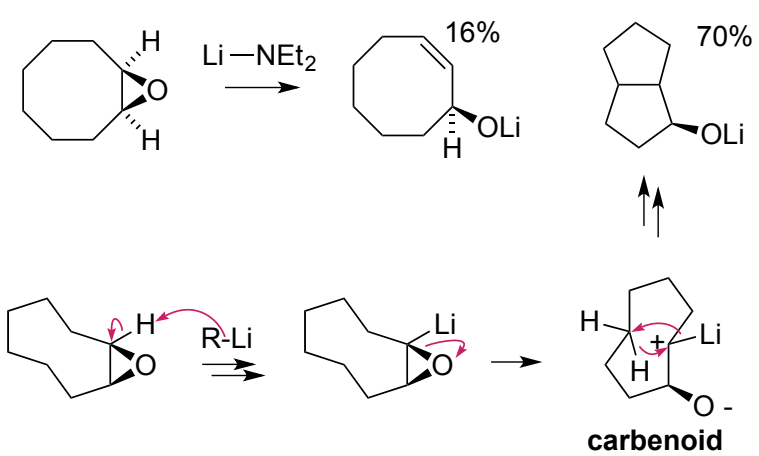
■ Epoxides undergo two competing reactions with bases

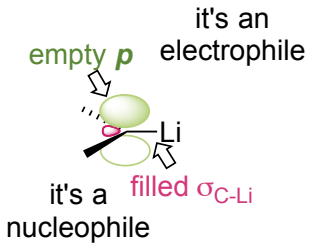
■ Lithium amide bases convert epoxides to allylic alcohols. The base removes the proton *syn* to the epoxide.



Thummel, R.P.; Rickborn, B. *J. Am. Chem. Soc.*, **1970**, *92,* 2064

■ Very aggressive bases deprotonate epoxides and generate **lithium carbenoids**.

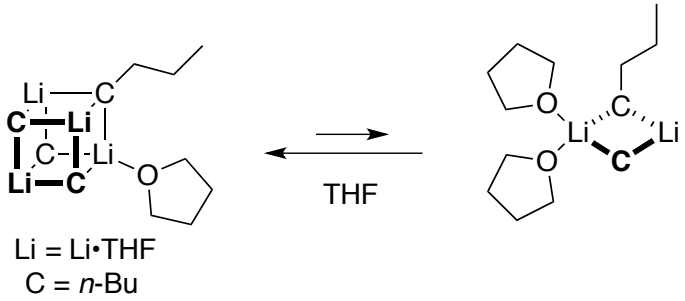




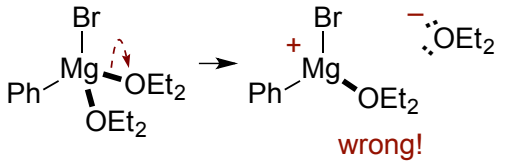
Cope, A. C.; Lee, H.-H.; Petree, H. E. *JACS* **1958**, *80*, 2849.
Hodgson, D.M.; Bray, C.D.; Humphreys, P.G. *Synlett* **2006**,1.

Aggregation of R-Li

■ Ether solvents coordinate to alkali metals. *n*-BuLi forms a tetramer in THF + some dimer

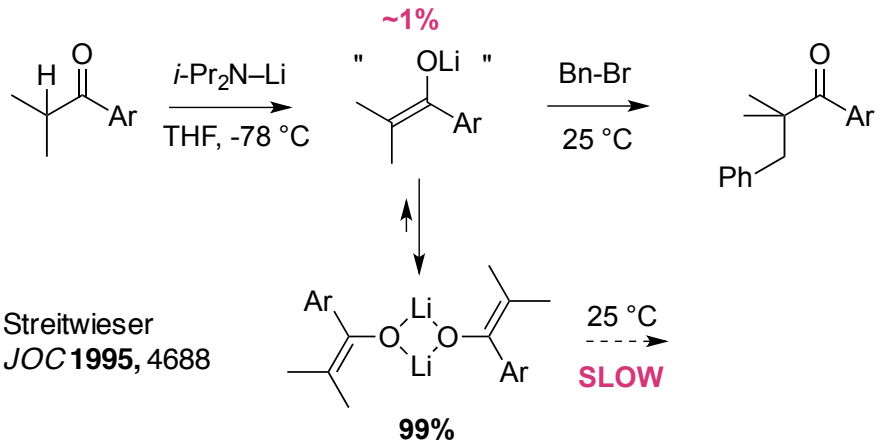


Li wants octet



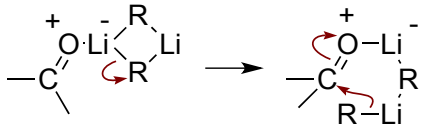
dative bonds to metals
don't draw charges
don't use for arrow pushing

■ Li enolates = 99% dimer in THF, **but reacts via monomer**.



Streitwieser
JOC **1995,** 4688

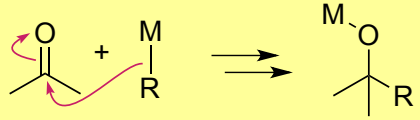
■ C=O Addition: Me—Li / *n*-Bu—Li add as dimer!



IMPORTANT RULE:

Arrow Pushers: *Pretend RM is monomer*

M = Li, MgBr



But never forget aggregation

Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y. D. *JACS* **1985**, *107*, 5560.
Nakamura, M.; Nakamura, E.; Koga, N; Morokuma, K. *JACS* **1993**, *115*, 110167.

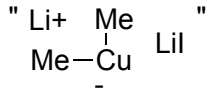
Organocuprates

■ Organocopper, R-Cu is not very nucleophilic or basic

■ **Cuprates,** R_2CuLi are ARE **nucleophilic.**
They do all the things you wished RLi could do: substn with R-X, opening epoxides, 1,4-addn., etc.
Require exquisite technique and involve complex mechanisms.

2 MeLi + Cu-I ⟶ **"Me_2CuLi" + LiI** *(Me_2CuLi = Gilman reagent)*

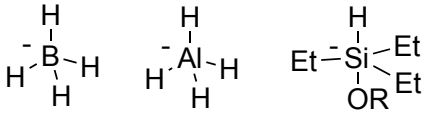
cuprate



actually, aggregated

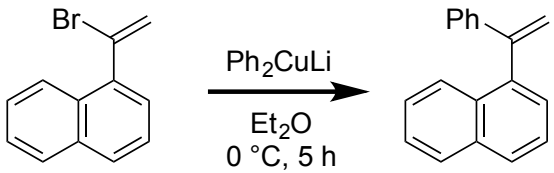
1. nucleophilic C
2. low charge on C
i.e., **SOFT**

borate *aluminate* *silicate*

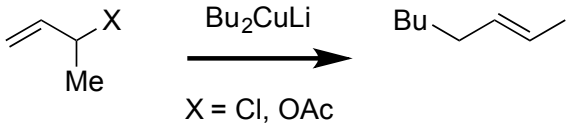


*other "-**ate**" complexes*
not soft

■ Cross-coupling

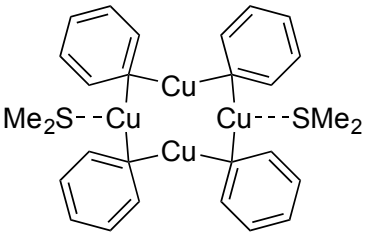


■ Cuprates favor **S_N2'**

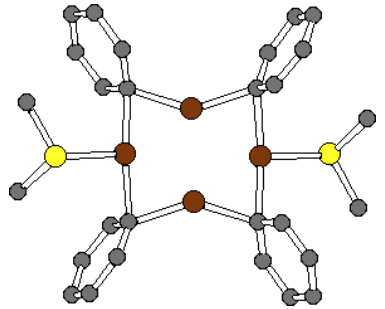


The true structures are complex

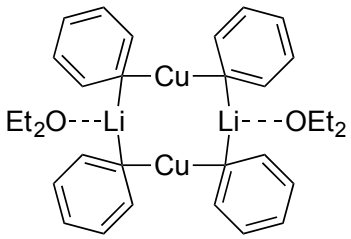
$PhCu \cdot 1/2Me_2S$

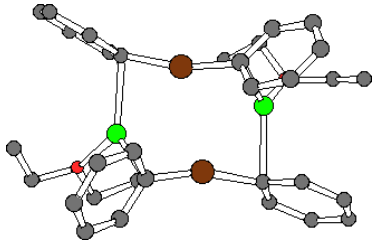


X-ray struct.



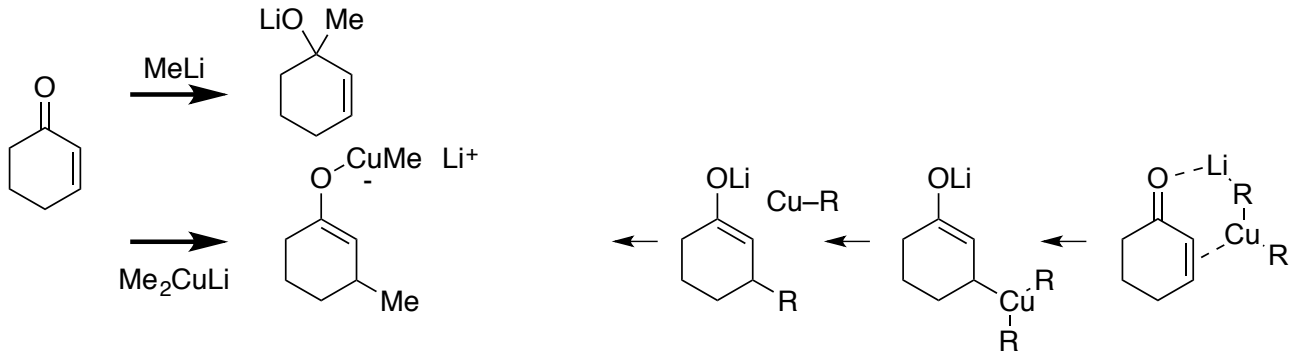
$Ph_2CuLi \cdot Et_2O$





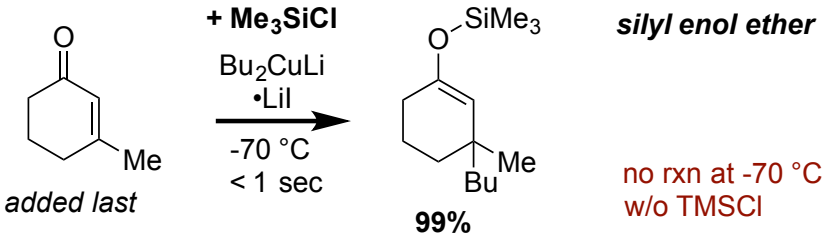
1,4 - Addition by Organocuprates

■ 1,4-Addition



Canisius, J.; Gerold, A.; Krause, N. *Angew. Chem. Int. Ed.* **1999**, *38*, 1644.

■ TMS-Cl accelerates 1,4 addn.

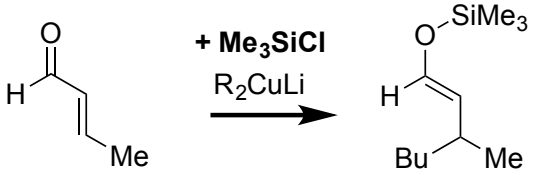


silyl enol ether

no rxn at -70 °C
w/o TMSCl

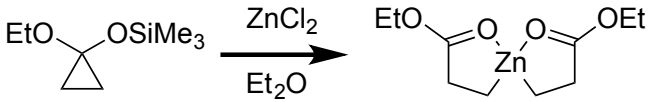
Nakamura, E.-I.; Kuwajima, I. *JACS* **1984**, 3368

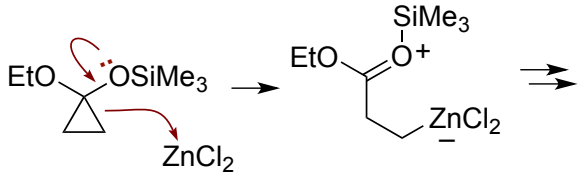
■ Cuprates add 1,4- to α,β-unsaturated aldehydes. All other organometallics would add to C=O.



Zinc Homoenolates

■ Nucleophilic cyclopropane bonds





Nakamura, E.-I.; Kuwajima, I. *JACS* **1986**, 27,83